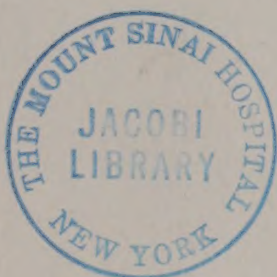
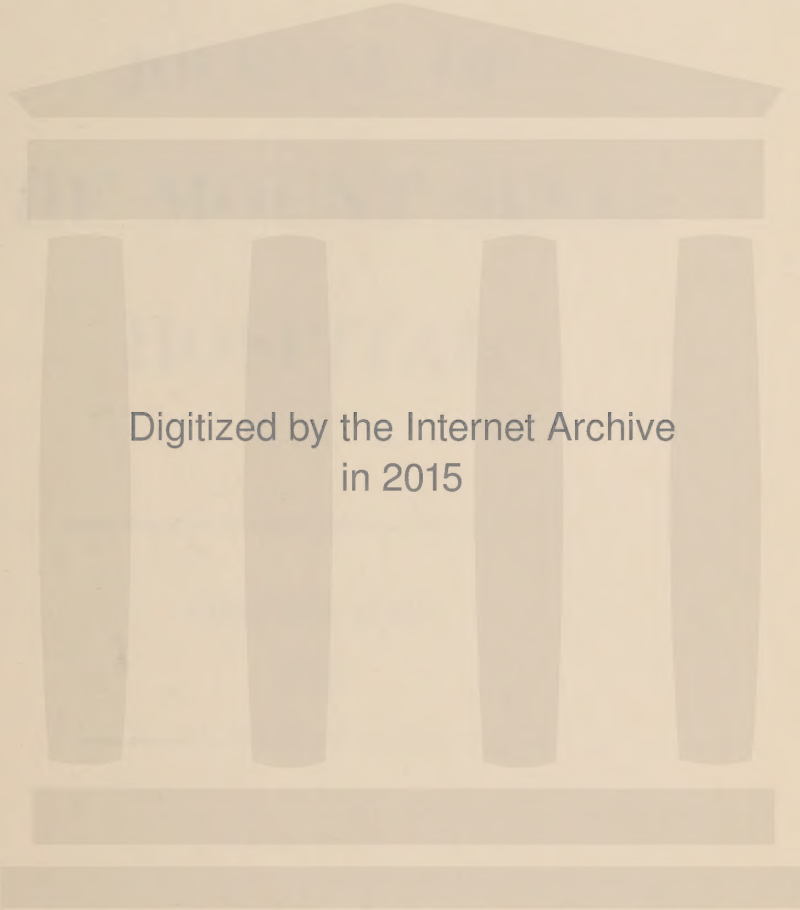




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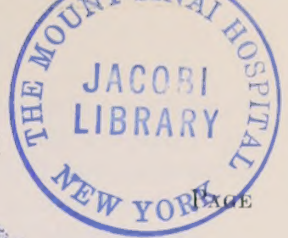
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In Memoriam

RICHARD LEWISOHN

1875-1961

With the death of Dr. Richard Lewisohn on August 11, 1961, The Mount Sinai Hospital has lost its Senior Consultant Surgeon, the medical profession an illustrious member, and his close colleagues a warm and loyal friend.

Dr. Lewisohn was born in Hamburg on July 12, 1875, where he received his preliminary education at the Real-Gymnasium and from where he entered medical school in Kiel in 1893. Following the German custom he attended several different medical schools and was graduated from the University of Freiburg with a Doctor's thesis on Malignant Tumors of the Kidney, in 1899.

After graduation he became an Assistant of Professor Carl Weigert, the world renowned Pathologist of the Senkenbergische Institute in Frankfurt-am-Main. He stayed for two years and published several articles of pathologic anatomic interest. In 1904 he became Assistant of Geheimrat Czerny, the Professor of Surgery at Heidelberg, where he remained until 1906 when he moved to New York. After having obtained his medical license, he joined the Surgical Staff at The Mount Sinai Hospital, where he advanced from Adjunct to Associate Attending Surgeon and became Attending Surgeon in 1928; he reached retirement age in 1937 and became Consulting Surgeon in the same year.

Dr. Lewisohn's claim to immortality is derived from his discovery of the Citrate Method of Blood Transfusion. The practice of blood transfusion had been applied in medicine for more than two centuries but it never had enjoyed wide use because of the hazards of the original procedure and the complexity of the later performance. After careful experiments on dogs, Dr. Lewisohn performed the first two transfusions in man with citrated blood and published the results in the January issue of the New York Medical Record of 1915. Simultaneously and entirely independently, Agote in Buenos Aires had published the identical solution of the problem by utilizing the lowest possible concentration of sodium citrate to prevent blood coagulation and to avoid toxic effects from citrate. It is amazing that this simple and logical device did not find immediate and universal acceptance. In spite of the many emergencies during the First World War, the citrate method of blood transfusion was hardly used by the Armed Forces and even after cessation of hostilities this method still had to compete with the older techniques of direct blood transfusion. Certain alarming side effects, such as chills, had to be investigated, and they were conquered in the early nineteen thirties. The possibility of storage of citrated blood greatly advanced its use in transfusion. At the beginning of World War II it had become the



DR. RICHARD LEWISOHN

1875—1961

exclusive method of blood transfusion used in surgery and medicine. Thus Richard Lewisohn could still witness the ultimate triumph of his discovery. And he received, although belatedly, the laurels he so well deserved. In 1955 he was the recipient of the Karl Landsteiner Award and Medal of the American Association of Blood Banks. In February, 1959, he was awarded an Honorary Fellowship in the Royal College of Surgeons of England and in the fall of the same year he became an Honorary Fellow of the American College of Surgeons. While the sponsors of these honors referred in their addresses mainly to his first great contribution, it had not been his last. Richard Lewisohn's mind did not retire and he was always on the alert to recognize new ideas and to apply them to urgent problems of surgery and medicine. For years the surgical treatment of peptic ulcer of the stomach and duodenum had been unsatisfactory. A new and radical operation had been advocated by Haberer of the University of Innsbruck. Dr. Lewisohn recognized the validity of the idea, but he was not unaware of the objection of exposing the patient to the risk of a dangerous operation for the treatment of a nonmalignant ailment which might yield to more conservative treatment. He traveled to Austria, acquainted himself with the operative technique and the results and became convinced of the justification of gastric resection for duodenal and gastric ulcer. His sound arguments persuaded Dr. A. A. Berg with whom he was associated on the first Surgical Service of The Mount Sinai Hospital to give the rather hazardous operation of gastric resection a trial. The results were most satisfactory and gradually the surgical profession all over the country became converted to subtotal gastrectomy as the method of choice for the treatment of peptic ulcer resistant to medical therapy. Richard Lewisohn had effectively served as Catalyst.

When the day of his retirement as an attending surgeon for age limit approached, he was far from ready for retirement. Now released from the arduous duties of an active surgical service, the time had come for him to return to the research laboratory, in which he had found so much satisfaction in the early years of his career. With his characteristic élan he surrounded himself with a staff of most competent investigators and began his romantic adventure in Cancer Research. For ten years he and his faithful collaborators explored the effects of splenic extracts and various vitamin and yeast extracts on the inhibition of growth of animal cancers. This is not the place to go into detail, but it should be recorded here that these investigations were the first to establish the significance of folic acid in the biology of the cancer cell.

In 1948 Richard Lewisohn felt that the time might also come for him to enjoy the blessings of restful years of retirement in the company of his beloved life companion Constance and surrounded by children and grandchildren. But at the age of eighty his scientific curiosity was reawakened. The high esteem in which he was held, had caused one of his intimate friends, Mr. Charles Guggenheimer, to persuade one of his clients to bequeath a sizeable sum of money to research work to be conducted at Richard Lewisohn's direction. When the money became available in 1954, Dr. Lewisohn felt that tissue research at the cellular and sub-cellular level might advance the science of medicine and he became the founder

of the Cell Research Laboratory at The Mount Sinai Hospital. For nearly five years he visited the laboratory almost daily. He remained inquisitive, enthusiastic and inspiring.

In presenting Richard Lewisohn for Honorary Fellowship in the Royal College of Surgeons of England, Sir Gordon Gordon-Taylor called his "safe and simple method of transfusing blood an epochal, momentous contribution . . . which has brought succour and health and healing to the sick and injured."

This tribute reflects the high esteem in which he was held by his fellow surgeons. For us who have known him more intimately it might be permitted to talk of him as a man. Richard Lewisohn had his faults; he was impatient. When his high ideals clashed with the conformity and trivialities of our age, he would sometimes become belligerent, and he made enemies and was proud of it. But he could even be prouder and fonder of those who gave him their admiration and their friendship. Because he deserved it as a man of the highest ideals, of unshakable convictions, of deep devotion to his friends and the highest loyalty to The Mount Sinai Hospital. We shall never forget him.

PAUL KLEMPERER, M.D.
MARJORIE LEWISOHN, M.D.
for the
Editorial Board

PATTERNS OF BONE CHANGE IN CLASSIC HEMOPHILIA AND CHRISTMAS DISEASE

JOHN E. MOSELEY, M.D.

New York, N. Y.

In recent years the subject of blood coagulation has become extremely complicated. A large group of specific circulating proteins, variously named and abbreviated, are now considered to be active in the coagulation mechanism (Table I). No attempt to discuss this mechanism in depth will be made here but some brief simplification of the modern concept of coagulation might be helpful for those who seldom have occasion to review recent advances in this phase of human physiology.

The end product of the coagulation process is the formation of insoluble fibrin, a tough, fibrous protein arranged in an interlacing network of strands within the interstices of which the blood cells are entrapped. Fibrin does not exist as such in the circulating blood but is formed in the process of coagulation from a soluble precursor, fibrinogen. The conversion of fibrinogen to fibrin takes place through the action of thrombin. It has been shown that the action of thrombin is that of a proteolytic enzyme splitting small polypeptide chains from the ends of each fibrinogen molecule. Thrombin does not circulate in the blood in any significant concentration but is present in the form of a precursor, prothrombin. The conversion of prothrombin to thrombin takes place through the action of thromboplastin and calcium. The exact mechanism by which thromboplastin alters the prothrombin molecule is as yet undetermined. It is known, however, that the interaction between thromboplastin and prothrombin involves the activity of three additional factors, namely, factor V (labile factor), factor VII (stable factor), and the Stuart-Prower factor.

At least three clinically important factors are necessary for the formation of thromboplastin. These specific thromboplastin precursors are antihemophilic globulin (AHG), plasma thromboplastin component (PTC, Christmas factor) and plasma thromboplastin antecedent (PTA). The development of thromboplastic activity takes place in the presence of calcium ions and platelets. Fig. 1 is a simplified schematic outline of the coagulation mechanism.

Diseases due to defects in blood coagulation have been classified as 1) those due to a deficiency of factors required for thromboplastin formation; 2) for conversion of prothrombin to thrombin and 3) those due to a deficiency of fibrinogen (1). Disorders in the first group, due to a deficiency of factors required for thromboplastin formation, are regarded broadly as the hemophilias. Until recently the term hemophilia was applied to a single disorder, that due to a deficiency of the antihemophilic globulin (AHG). The discovery of the other two thromboplastin precursors, PTC (Christmas factor) and PTA, resulted in the realization that hemophilia was indeed not a single entity but a group of entities

* From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

with similar symptomatology. The disorder due to deficiency of antihemophilic globulin (AHG) is regarded as classic hemophilia or hemophilia A. The condition resulting from a deficiency of plasma thromboplastin component (PTC or Christmas factor) has been called Christmas disease or hemophilia B, and that due to a deficiency of plasma thromboplastin antecedent (PTA) is referred to as hemophilia C. All three conditions occur as hereditary abnormalities and show a bleeding tendency from childhood. Classic hemophilia and Christmas disease are inherited as sex-linked recessives, are confined almost exclusively to males and are transmitted by carrier females. In contrast, PTA deficiency (hemophilia C) is transmitted as a dominant with no sex-linkage and affects both males and females.* Classic hemophilia and Christmas disease are clinically practically

TABLE I
Some of the Coagulation Factors and Their Various Designations

Coagulation Factors	Synonyms	Abbreviations
Antihemophilic globulin	Factor VIII Thromboplastinogen	AHG, AHF
Plasma thromboplastin component	Factor IX Christmas factor	PTC
Plasma thromboplastin antecent		PTA
Labile factor	Factor V Plasma accelerator factor Proaccelerin Plasma Ac-globulin	
Stable factor	Factor VII Proconvertin Prothrombin conversion factor	SPCA
Stuart-Prower factor	Factor X	

indistinguishable. Bleeding into bones and joints is characteristic of both conditions. On the other hand, in PTA deficiency the bleeding tendency is only slight and bone and joint involvement rarely occurs. Severe hemarthrosis is also unusual in the other hemorrhagic diseases. An analysis of the bone and joint changes in hemophilia, therefore, is essentially limited to consideration of classic hemophilia and Christmas disease. Since these two conditions are so similar in clinical and radiographic manifestations, management and prognosis, they will be referred to below merely as hemophilia.

The symptoms of hemophilia usually begin in infancy and tend to be most severe before puberty. Of 56 cases reviewed by Jordan (2), the clinical onset

* A recent study (16) appears to show that the gene for PTA deficiency is an incompletely recessive or "intermediate" gene which produces major PTA deficiency in the homozygote and minor PTA deficiency in the heterozygote.

of the disease occurred during the first year of life in 44 of them. The first indication of the disorder was in the form of subcutaneous, intramuscular, intra-articular or internal hemorrhage.

Unlike purpura hemorrhagica, the bleeding is considered by many always to be due to trauma, however mild, and not to spontaneous hemorrhage. In many instances, nevertheless, a definite history of trauma cannot be obtained. The tendency to hemorrhage appears to diminish in patients who survive to adult life but it is possible that this reflects only the patient's increased ability to avoid major and minor injuries.

Although hemophilia is characterized by recurrent episodes of bleeding in various parts of the body, the most characteristic site of hemorrhage is into the joint cavities. Hemarthrosis is so common in classic hemophilia and Christmas disease, in fact, that its absence in patients who reach adult life is consid-

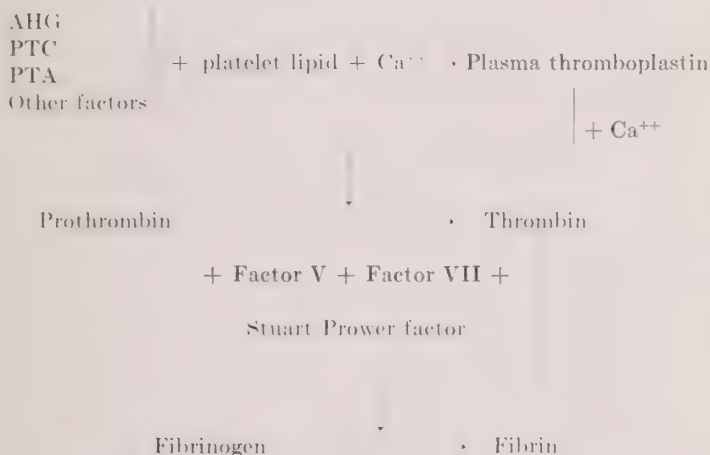


FIG. 1. Simplified Schematic Outline of the Coagulation Mechanism

ered to raise some question as to the diagnosis (3). There is a mild form of hemophilia, however, in which symptoms may not appear until the patient is four or five years of age or older. In this mild form bleeding may follow dental extractions, tonsillectomy or other surgical procedures but may not result from everyday injuries (4). While in such patients rather severe hematomas may develop in the soft tissues, hemarthroses seldom occur and significant joint changes are rarely ever seen. The diagnosis of this mild form of hemophilia is often quite difficult and frequently delayed. Actually, the severity of symptomatology in hemophilia tends to parallel the degree of deficiency of the clotting factor. Thus, in severe classic hemophilia there appears to be an almost total absence of the antihemophilic globulin while in mild hemophilia the antihemophilic globulin factor may be found to be as high as five or ten per cent of the average normal values (5). A similar ratio probably exists between the severity of symptoms and the concentration of Christmas factor in Christmas disease.

The bone and joint changes which may be demonstrable radiographically in

hemophilia may be due to 1) *intra-articular*; 2) *intra-osseous* and 3) *subperiosteal hemorrhage*. The various radiographic patterns of bone change depend on the site of the hemorrhage, the amount of bleeding and its chronicity and, of great importance, the age at which these pathological phenomena take place. Intra-articular hemorrhages and their resulting arthropathies provide by far the commonest roentgen findings in hemophilic patients.

HEMOPHILIC ARTHROPATHIES

Hemorrhage may occur into any joint but the knees, elbows and ankles are involved much more commonly than the other articulations. In all reports the knees are the most frequently affected joints. Caffey and Schlesinger (6) have suggested that this may well be due to the relative vulnerability of the knees to injury and to the difficulty of protecting these articulations in walking. Among the 56 patients studied by Jordan (2) the total number of major joints affected was as follows: Knees 97, elbows 72, ankles 52, shoulders 16, hips 16 and wrists 15. While only a single joint may be involved at the time of any given examination, observation of hemophiliacs over a protracted period will show that in the majority of them multiple joint involvement eventually develops. In the vast majority of cases the first major joint to become involved is the knee. In about half as many cases the first joint affection involves multiple joints. Only occasionally is the elbow, ankle, hip or shoulder the first single site of involvement. The hemarthropathies tend to develop prior to adolescence. Thomas (7) has reported a study in which in 89 per cent of 98 hemophilic patients with hemarthrosis the clinical evidence of joint involvement developed before the age of ten years.

Clinically in the acute hemarthroses there is rapid swelling, heat, various degrees of tenderness and limitation of motion. Discoloration around the joint is relatively uncommon. With the cessation of bleeding the blood within the joint is gradually absorbed and there is slow restitution of joint mobility. Once a joint has been the site of hemorrhage, however, bleeding tends to recur and to eventuate in permanent and often crippling deformities.

The very nature of this hemorrhagic disease makes a complete knowledge of the pathology of its various phases difficult to acquire. Pathological examination of involved tissues is essentially limited to the tissues available at autopsy. Opportunities to study such tissue at the operating table or from biopsy specimens are obviously rare. Early descriptions of the pathological anatomy of hemophilic arthropathy were followed by detailed microscopic studies of the synovia and subsynovial tissues by Key (8) in 1932. More recently Swanton (9) has made some excellent studies on the various stages of hemarthrosis in a colony of hemophilic dogs. This canine hemophilia appears to be identical with the human disease both in regard to the nature of the clotting defect and the pattern of inheritance and it is likely that the pathological changes observed are essentially similar to those which occur in humans. Analysis of the roentgen findings in affected bones and joints has also contributed to our understanding of the pathological processes involved.

In the early stage of hemophilic arthropathy, after the initial or early hemarthroses, there is an increased density of the periarticular soft tissues usually with distention of the joint space (Fig. 2). When the hemorrhage is of considerable degree the distended joint space may be seen to compress the adjacent soft tissue shadows (Fig. 3). There is nothing distinctive about this appearance, however, and the findings are similar to those which may be found in nonhemophilic hemarthrosis or synovitis. There is no abnormality demonstrable in the architecture of the regional bones. These early hematomas may organize and be absorbed with no residua.

When, after the initial or repeated hemorrhages, the intra-articular blood is not completely absorbed, the retained blood or blood clots produce a chronic synovitis. There is a villous hyperplasia of the synovium and a dense layer of subsynovial fibrous tissue develops. The periarticular soft tissues become thickened. This results in varying degrees of limitation of motion. Key (8) has called attention to the fact that at this stage recurrent hemorrhage is attended by smaller articular swellings because the heavy subsynovial fibrous tissue prevents extreme distention of the joint space. Increased density in and about the joint is enhanced by the deposition of hemosiderin in the soft tissues. As a result of the local hyperemia and associated disuse the regional bones become osteoporotic, often markedly so (Fig. 4).

Encroachment by the thickened synovial membrane results in erosion of the articular cartilage at its margins and irregular areas of destruction may occur in the more central portions of the cartilage. Subchondral bone erosion develops in areas underlying damaged cartilage or possibly as a result of subchondral hemorrhage (Figs. 5, 6). Cartilage destruction also results in varying degrees of narrowing of the interosseous space (Figs. 7, 8). As the process progresses numerous juxta-articular cysts, irregular in distribution and size, develop (Figs. 9-11). These represent one of the characteristic findings in hemophilic arthropathy. It is generally considered that these cysts are the result of hemorrhage into the subchondral bone but the recent studies of Swanton (9) have shown that in canine hemophilic arthropathy such cysts are lined by a single layer of synovial cells and the bulk of the lucent area consists of dense fibrous tissue with very little or no evidence of blood pigment. Her findings would suggest that these subchondral cysts may be more related to premature degenerative changes in the articular cartilage and subchondral bone than to subchondral bone hemorrhage. Possibly both mechanisms are involved. At any rate, such multiple cysts are seen in joints, such as the elbow, in which they seldom occur in the more common forms of osteoarthritis and they tend to be greater in number and larger in size than in other arthropathies (Figs. 12, 13). In some areas the cysts communicate with the joint cavity at a site of cartilage or bone erosion. Concomitant with destruction of the interosseous space and the development of numerous subchondral cysts there is usually some eburnation of the articular cortices and subchondral bone sclerosis (Figs. 10, 11). Although multiple subchondral cyst formation is usual and characteristic in long-standing hemophilic arthropathy in some instances the arthropathy may reach quite ad-



FIG. 2. Ankles of a 2½ year old patient with AHG deficiency. The right ankle is the site of an initial hemarthrosis. The joint spaces are distended and increased in density due to hemorrhage. There are no abnormalities of the bones. The pseudocystic radiolucent triangles seen in both os calci are due to a deficiency of spongy bone which is of no pathological significance.



FIG. 3. Knee of a 6 year old hemophilic with VIII deficiency. There has been a large hemorrhage into the joint. The quadriceps tendon is compressed and displaced ventrally and the infrapatellar fat pad is encroached on from behind by the distended joint space.

vanced stages without cyst formation (Fig. 14). Deeper in the cancellous bone, away from the joint surface, larger bone cysts may develop which in all likelihood are the result of intra-osseous hemorrhage.

Over a period of time continued use of an affected joint and weight-bearing further increase the degenerative changes and osteophytosis develops. The osteophyte formation may be extensive and in some cases even bizarre (Fig. 15).



FIG. 4. This is the knee shown in Fig. 3 sixteen months later. The periarticular soft tissues are thickened. There is a marked osteoporosis of the femoral and tibial epiphyses and of the patella.

Occasionally a joint may be deformed by hemorrhage into the epiphyseal cartilage at the growth zone (10). This results in slipping of the epiphysis and premature fusion of the epiphysis in an abnormal position (Fig. 16). The in-

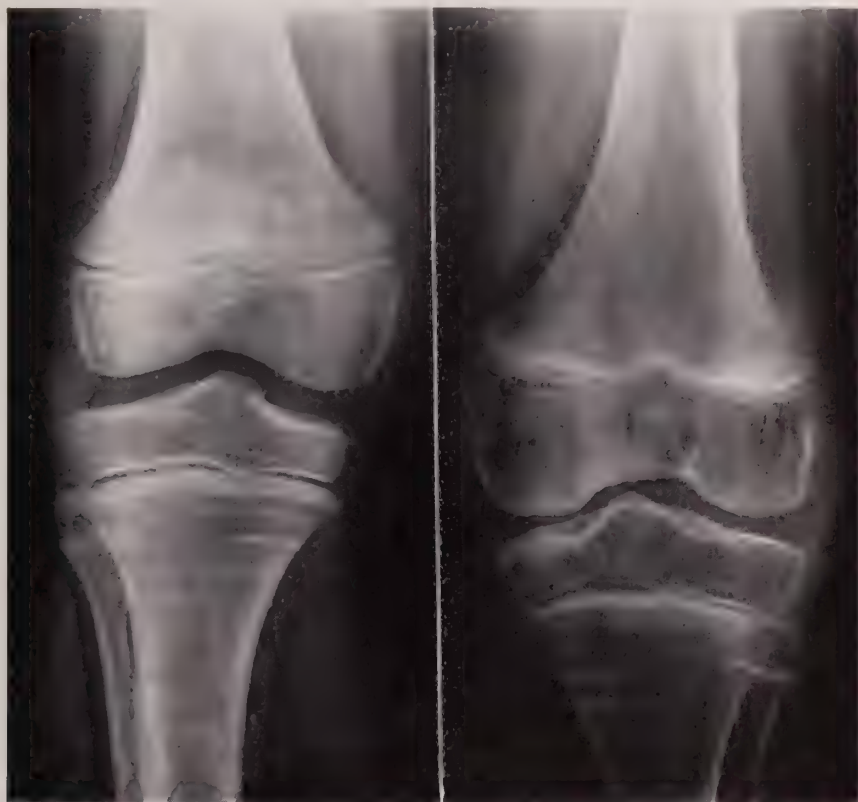


FIG. 5. Knees of a 9 year old hemophiliac with pte deficiency. There are subchondral bone erosions on the articular surface of the left tibial epiphysis. The regional bones are osteoporotic and the left femoral and tibial epiphyses are enlarged. The left knee has been the site of repeated hemorrhages. There is a series of growth lines in the femoral and tibial metaphyses on both sides. The spaces between these transverse lines are deeper on the left side where growth has been accelerated due to chronic hyperemia.

stances of this type of deformity which we have seen have occurred mostly at the shoulders.

SPECIAL ROENTGEN FEATURES

Most of the roentgen changes described above which occur in hemophilic arthropathy may be found not uncommonly in various other joint affections. There are some changes frequently seen in the hemophilic joint, however, which are uncommon in most other arthropathies and some which are rarely, if ever, seen in other conditions.

Enlargement, Dysgenesis and Accelerated Maturation of the Epiphyses: In the growing skeleton, presumably due to chronic hyperemia, there may be premature ossification of the epiphyses. The epiphyses may enlarge rapidly compared to those of unaffected joints (Figs. 5, 6, 17). Frequently there is premature fusion of the epiphyses at the affected joint. Accelerated epiphyseal growth and maturation may also be seen in juvenile rheumatoid and tuberculous arthritis and

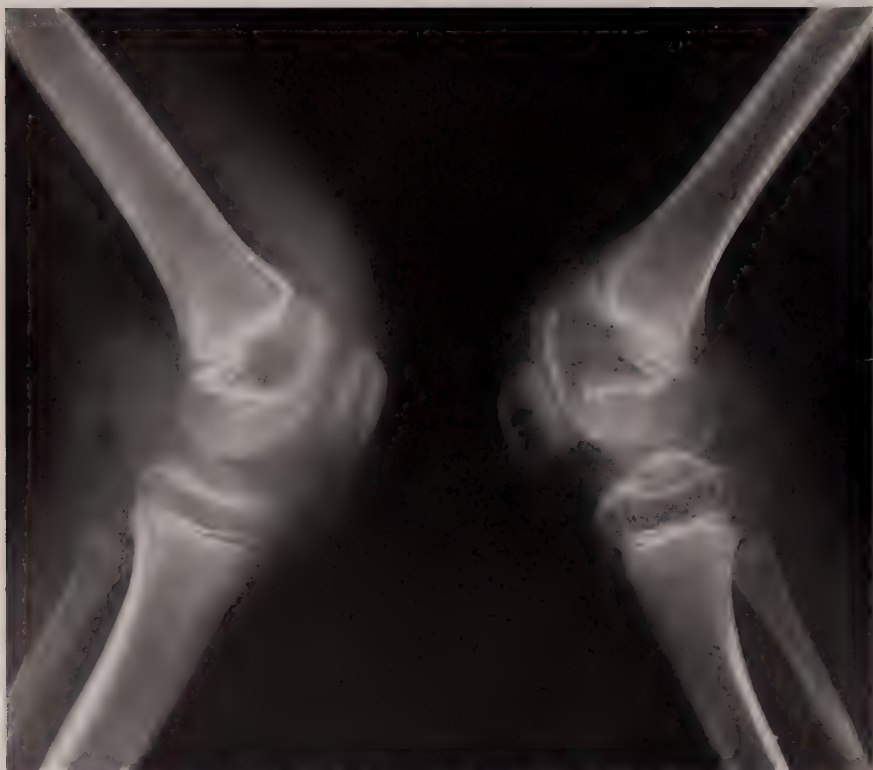


FIG. 6. Knees of patient with classic hemophilia. The right knee is the site of early hemorrhage. The periarticular soft tissues are increased in density and the joint space is distended. There are no alterations of the regional bones. The left knee has been involved by recurrent hemorrhages with incomplete absorption of the hematomas. The periarticular soft tissues are thickened. The femoral and tibial epiphyses are enlarged and porotic. The patella is losing its rounded inferior apex. There are early erosions of the femoral and tibial articular surfaces.

in healing fractures at or near the joint. In some cases of hemophilia there is dysgenesis of an epiphysis associated with its accelerated maturation. In such instances the epiphysis is deformed and flattened. Epiphyseal dysgenesis is most commonly seen at the head of the radius. Enlargement and dysgenesis of the proximal radial epiphysis occurring in childhood results in a rather characteristically large and misshapen radial head in the adult (Figs. 12, 13, 18).

Marked Osteoporosis and Changes in Trabecular Pattern: In young individuals with hemophilic arthropathy osteoporosis tends to be unusually severe and involves the epiphyses to the extent that their extreme lucency may stand out



FIG. 7. Knee of patient with AHG deficiency. There are subchondral erosions of the articular surfaces. The interosseous space is narrowed due to cartilage destruction. The epiphyses are porotic and there is coarsening of their trabeculae. The intercondylar notch is widened.



FIG. 8. Knee of 14 year old hemophiliac. There is subchondral erosion of the femoral and tibial articular surfaces. Cartilage destruction has resulted in marked narrowing of the interosseous space. The epiphyses are markedly porotic and their trabeculae are coarsened and show some early disorganization.

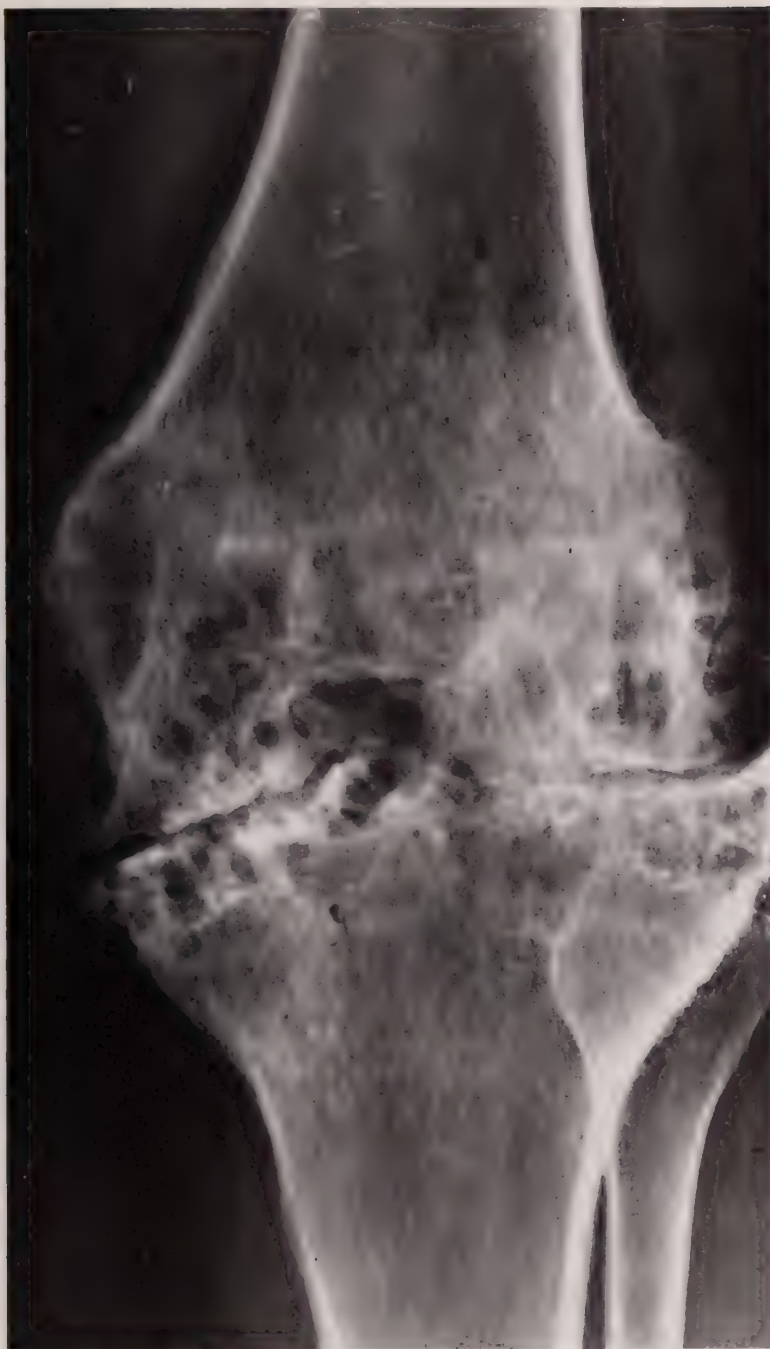


FIG. 9. Advanced hemophilic arthropathy in a 40 year old patient. The articular cartilage has been almost completely destroyed. The interosseous space is markedly narrowed. There is erosion of the articular cortices and there are numerous subchondral cysts of varying sizes in the femoral and tibial metaphyses. Osteophyte formation has taken place at the articular margins of both bones. The intercondylar notch is widened.

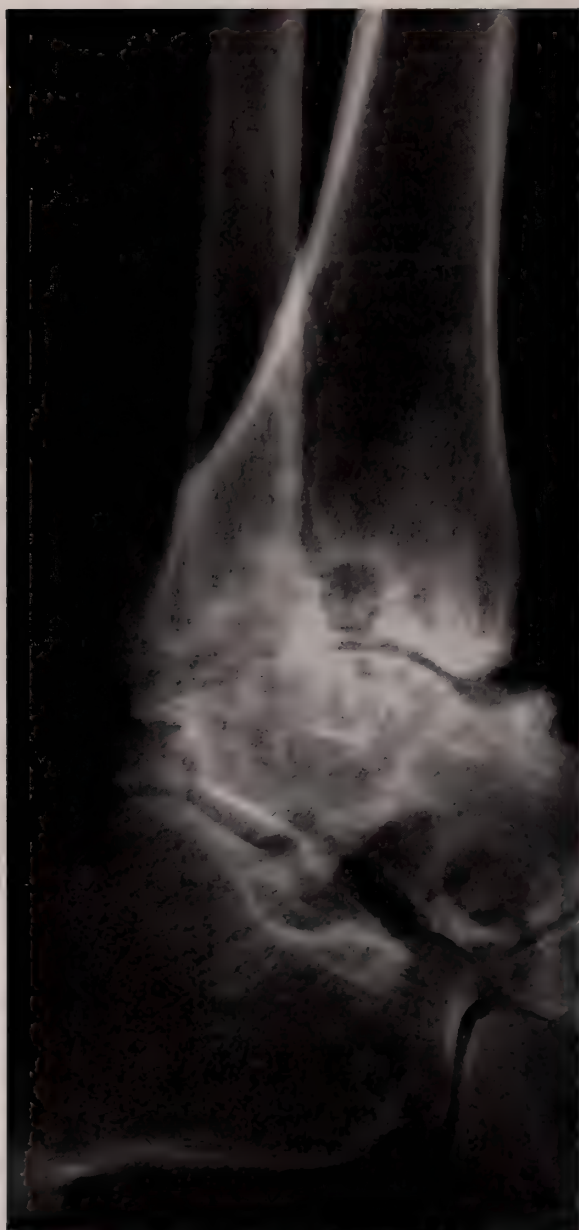


FIG. 10. Ankle of adult hemophiliac with advanced hemarthropathy. The tibiotalar interosseous space is considerably narrowed due to cartilage destruction. There are numerous subcortical cysts. The articular cortex is eburnated and there is diffuse subcortical sclerosis. A large subcortical cyst is seen adjacent to the talonavicular joint.



FIG. 11. Advanced hemophilic arthropathy in adult. The radiocarpal joint is practically obliterated. The opposing articular surfaces are eroded and there are numerous subchondral cysts at the distal end of the radius and in the navicular and lunate bones. Cortical eburnation and subcortical sclerosis are evident.

against the relative density of the adjacent bone (Fig. 8). As the arthropathy progresses the epiphyseal trabeculae tend to assume a radial striation parallel to the long axis of the shaft. Similar changes may be seen in juvenile rheumatoid and tuberculous arthritis. In advanced cases there may be a characteristic disorganization of the epiphyseal and adjacent metaphyseal trabeculae.

The "Squared-Off" Patella: In most cases of advanced hemophilic arthropathy the distal apex of the patella is flattened. In the earlier stages of the arthropathy the patella participates in the acceleration of growth and enlarges accordingly. As the condition advances, however, the distal portion of the patella loses its tapered form and the end of the bone flattens out resulting in the appearance of

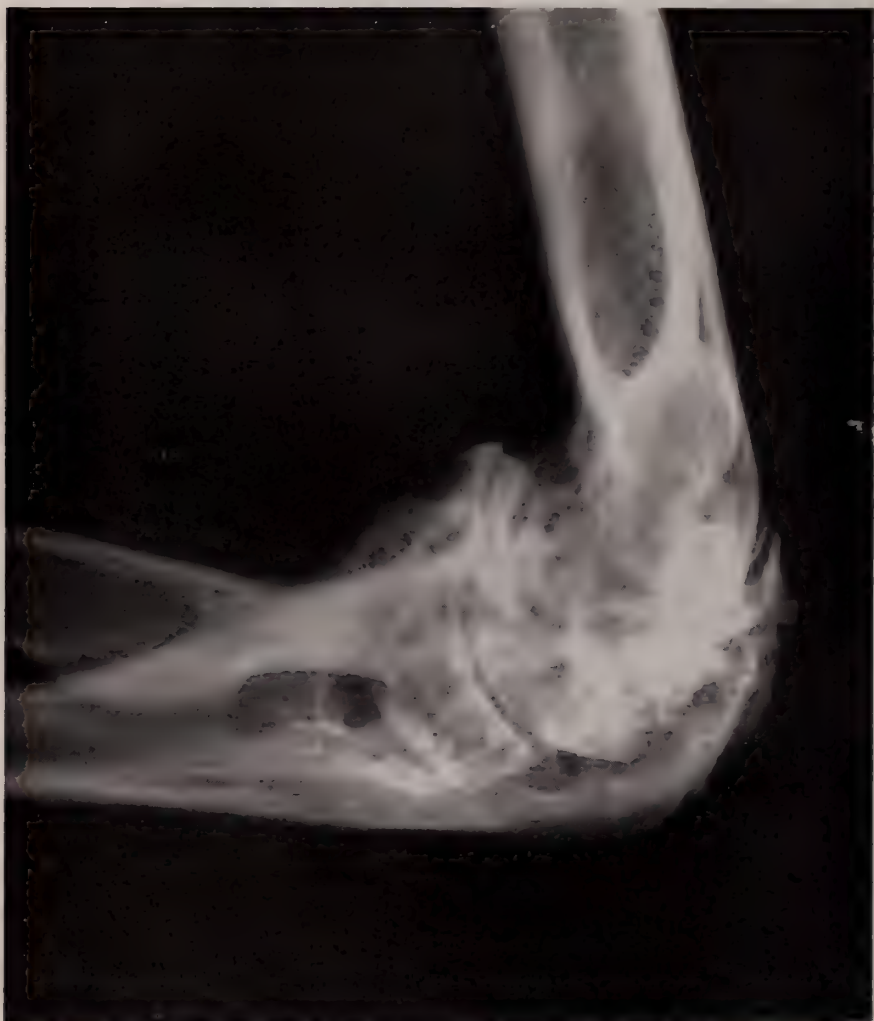


FIG. 12. Advanced hemophilic arthropathy at elbow of adult with AHG deficiency. The interosseous space between the humerus and the radial head is markedly narrowed. The anterior surface of the olecranon process is irregularly eroded. Numerous subcortical cysts are seen in the distal humerus and in the head of the radius. The radial head is greatly enlarged and flattened due to earlier epiphyseal dysgenesis and accelerated growth.

FIG. 13. Elbow of patient with AHG deficiency. There is a large pseudocystic area of bone destruction extending subcortically deep into the lateral epicondyle of the humerus. Numerous smaller cysts of varying sizes are seen in the juxta-articular portions of the bones. There has been partial destruction of the articular cartilages. The radial head is widened and flattened.



FIG. 13

the "squared-off" patella (Figs. 19-22). Jordan (2) considers this peculiar development to be due to premature cessation of growth affecting mostly the distal segment of the patella. This possibly is so but whatever the nature of this change may be, the appearance of its advanced form is one which we have never seen in any other arthropathy and which may be considered highly suggestive, if not diagnostic, of hemophilia. This unusual change is not seen in arthropathies which are late in origin but is common in cases where severe recurrent bleeding has occurred at an early age.



FIG. 14. Knee joint of patient with advanced hemophilic arthropathy. The interosseous space is practically obliterated but typical subchondral cyst formation has not developed.

Widening of the Intercondylar Notch: Following repeated hemarthroses the intercondylar notch widens, often with an irregular contour (Figs. 7, 9, 23). The mechanism of this defect is not quite clear. It may be due to hemorrhage into the attachment of the cruciate ligaments as suggested by Jupe (11) or to erosion similar to that which occurs on the other bony surfaces uncovered by cartilage. The appearance is distinctive, seldom seen in other conditions and characteristic of hemophilic arthropathy.

Number and Variation in Size of Subchondral Bone Cysts: Subchondral bone cysts may be seen in other arthropathies, notably the common osteoarthritis but rarely does one find these cysts in such profusion and with such variation in size as is seen in the hemophilic joint. In addition, they may be found in great numbers in joints such as the elbow where they are seldom seen in the more common arthropathies (Figs. 12, 16). It is often possible, at a glance, to sug-



FIG. 15. Knee of patient with advanced hemophilic arthropathy. The interosseous spaces are narrowed and there is diffuse subchondral cyst formation. Large bizarre osteophytes extend from the posterior articular margins of the femur and tibia.

gest the diagnosis of hemophilia by the sheer exaggerated number of such cysts seen at an affected joint.

INTRA-OSSEOUS HEMORRHAGE

It is considered by many that the characteristic subchondral cysts in hemophilia are the result of intra-osseous hemorrhage in the subchondral bone. Swan-

ton (9) has cast some doubt on this concept of the formation of these lucencies. It is possible, however, that both degenerative change and hemorrhage may be involved in the production of these lesions.



FIG. 16. There is a mild humerus varus at the shoulder of an adult hemophiliac. The number and size of the subchondral cysts would be unusual for this joint in the more common varieties of osteoarthritis. The position of the humeral head has probably resulted from slipping and premature fusion due to hemorrhage into the epiphyseal cartilage during the earlier stages of the arthropathy.

Hemorrhage may occur also in a long bone near a joint or some distance from it (Fig. 24). Lytic lesions of various sizes, due to hemorrhage, may develop in round and flat bones as well.

When hemorrhage occurs in an epiphysis it may result in a lytic or "cystic" lesion or there may be collapse of the epiphysis, especially at a weight-bearing

joint, with the production of an appearance which cannot be distinguished from aseptic necrosis of other etiology (Figs 25, 26). At the hip such an involvement of the capital femoral epiphysis may be difficult to distinguish from Legg-Perthes disease, sickle cell infarction, Gaucher's disease, hypothyroidism and the numerous conditions associated with coxa plana. If there have been repeated hemorrhages into the joint, however, there are apt to be an associated narrowing



FIG. 17. Knees of a young hemophiliac. The right knee was the site of the original hemarthrosis and joint changes are more advanced on this side. Hemorrhage into the left knee has been more recent. Note that the right femoral and tibial epiphyses are larger than those on the left side and that the porosis is greater on the right side. The spacing between the transverse growth lines is also greater on the right side indicating accelerated growth on this side. These changes are due to a longer duration of chronic hyperemia at the right knee.

of the interosseous space and varying degrees of erosion of the articular cortex of the acetabulum. An associated soft tissue mass at the joint may occasionally be seen. When the associated changes of chronic hemarthrosis are not present the epiphyseal lesion is not radiographically distinctive.

SUBPERIOSTEAL HEMORRHAGE

Strangely enough, subperiosteal hemorrhage is not common in hemophilia. Occasionally, especially in children, there may be a minimal periosteal reaction



FIG. 18. There is marked enlargement and flattening of the head of the radius in an adult patient with advanced hemophilic arthropathy.



FIG. 19. Hemophilic arthropathy. There is a "squared-off" patella. The inferior pole of the patella has lost its normal apical contour and is flattened.

seen along the shaft of a long bone adjacent to a hemarthrotic joint. This is a reaction to hyperemia and not the result of subperiosteal hemorrhage. When subperiosteal hemorrhage does occur it may resemble subperiosteal hemorrhage as seen in other conditions. In this instance the roentgen appearance is charac-



FIG. 20. Advanced hemophilic arthropathy with "squared-off" patella.

terized by gradual calcification of the hematoma, the laying down of periosteal new bone, resorption and eventual resolution with or without slight residual cortical thickening in the involved area. In some cases, however, subperiosteal hemorrhage may be of such a degree that considerable pressure is exerted on the



FIG. 21. Advanced hemophilic arthropathy with "squared-off" patella.



FIG. 22. Hemophilic arthropathy with "squared-off" patella.

adjacent cortical bone. The underlying cortex may become eroded by pressure atrophy. Bony spicules may develop in the hematoma perpendicular to the cortex and scattered calcifications may develop within the organizing blood mass. In addition, at the edges of the hematoma where the periosteum begins its eleva-

tion from the cortex, periosteal new bone is formed giving an appearance similar to the cuff or triangle considered characteristic of malignant tumor (12). These features, developing in hemophilic subperiosteal hematoma, have been mistaken for bone sarcoma with disastrous results. This combination of roentgen features in hemophilia has been referred to as *hemophilic pseudotumor*. Most of the



FIG. 23. Hemophilic arthropathy showing irregular widening of the intercondylar notch at the knee.

long bone pseudotumors have occurred in the femur. Often there are evidences of chronic hemarthrosis at the nearest joint and in such instances one may suspect a relationship between the two lesions. At any rate, it is important to appreciate that changes resembling sarcoma can and do occur following subperiosteal hemorrhage in hemophiliacs.

Another type of pseudotumor which may occur in hemophilia is that involving large areas of the iliac bone on one or both sides of the pelvis. This complication of hemophilia may be classified under subperiosteal hemorrhage because al-



FIG. 24. Shoulder of hemophiliac with ptc deficiency. There is a rounded area of bone destruction at the humeral tuberosity due to intra-osseous hemorrhage.

though the exact site of the hemorrhage and the nature of the process producing osteolysis are uncertain, the evidence available from autopsy of the few reported cases would *suggest* that the lesion is primarily due to subperiosteal bleeding. Interesting reports on such iliac lesions have been made by Silber and Christen-



FIG. 25. Hemophilic arthropathy of the hip. There is a large area of bone destruction in the femoral epiphysis due to hemorrhage in the subchondral bone.

sen (13), Fraenkel, *et al.* (14), and Horwitz and his associates (15) among others. These lesions are usually accompanied by large soft tissue masses and are painless. Frequently there is a history of a painless swelling of several months' or even years' duration. Some patients have recalled a trauma to the hip or flank some months previously. Others have been unable to remember any such local trauma.



FIG. 26. Hip of hemophiliac with $\Delta H G$ deficiency. The interosseous space is narrowed and the articular cortex of the acetabulum is eroded. There is an aseptic necrosis of the femoral head due to hemorrhages in the bone. With continued weight bearing the epiphysis may collapse with resulting coxa plana.

The roentgen appearance is that of an extensive irregular area of destruction in the wing of the ilium. This is usually associated with a large soft tissue mass which may displace fragments of ilial bone and induce the production of periosteal new bone. Varying degrees of calcification, usually minimal, may be seen within the soft tissue mass. In the earlier stage of its evolution the bony defect



FIG. 27. There is a large hemophilic pseudotumor of the right ilium in a young adult with X^{H} deficiency. Strands of periosteal new bone are present over the anterior and lateral aspects of the defect and minimal hazy calcifications are seen within the area of destroyed bone. There is no associated soft tissue mass. A large subchondral cyst is noted at the acetabulum and there is a large soft tissue mass (hematoma) in the right flank.

may show bony septa which crisscross the osteolytic area. In a case which we have followed (Fig. 27) the septa disappeared over a period of about eighteen months. In this instance there was no soft tissue mass associated with the bone lesion but a large hematomatous mass was present in the flank. Horwitz, Simon and Bassen (15) have reported a pseudotumor involving the right pubis.

The radiologist, presented for the first time with films showing hemophilic bone or joint changes, has usually already been alerted to the diagnosis by the referring physician. In occasional cases, however, intra-articular, intra-osseous or subperiosteal hemorrhage may be the first and only sign of hemophilia. In other instances minor episodes of bleeding may have been overlooked or unreported to the physician. Under such circumstances the radiographic diagnosis of hemophilic bone and joint disease may be difficult. It is important, therefore, for the radiologist to be familiar with the various patterns of bone and joint change which may occur in this condition. While in some phases of skeletal involvement the changes may be nonspecific, it is nevertheless necessary to consider hemophilia in the differential diagnosis of such a roentgen appearance. On the other hand, attention has been called above to certain special roentgen features which are characteristic of hemophilia and which should lead to immediate hematologic investigation. In the case of pseudotumors, failure to recognize their possible hemophilic nature may result in biopsy or other surgery disastrous to the patient.

Perhaps the most significant aspect of the roentgen examination in hemophilic bone and joint disease is the information it provides for guidance in orthopedic rehabilitation. Few hemophiliacs who survive the first few years of life are spared the destruction of one or more joints from hemorrhage. Jordan (2) who has worked extensively in the rehabilitation of these patients has noted the importance of roentgen examinations in the following statement. "The significance of the x-ray picture, however, lies in the information which we can obtain regarding the degree of bone and joint involvement, the maturity of the skeleton at the time of the examination, the degree of deformity already present and the degree of additional deformity to be expected from further growth of the skeleton prior to maturity. The extent of generalized decalcification and the number and size of juxta-articular cysts will suggest the degree of softening of the bone. These factors will determine the plan for corrective treatment with plaster of Paris casts and orthopedic appliances."

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AN APPRAISAL OF FREE WATER REABSORPTION (T^cH_2O) IN MAN

GILBERT M. EISNER, M.D.,* JEROME G. PORUSH, M.D.,* MARVIN H.
GOLDSTEIN, M.D.* AND MARVIN F. LEVITT, M.D.

New York, N. Y.

In 1951 and 1952 Smith (1, 2) and Wesson and Anslow (3) introduced the concept of free water reabsorption (T^cH_2O), i.e. that quantity of solute-free water abstracted per minute from an isosmotic tubular fluid to concentrate the urine. In the presence of maximum antidiuretic hormone (ADH) activity, distal tubular fluid was presumed to be isotonic upon entering the collecting duct. Thereafter, the abstraction of solute-free water, allegedly by an active process, served to concentrate the urine. In studying the characteristics of osmotic diuresis Smith and co-workers proposed that at low rates of urine flow active water reabsorption was limited by a maximum urine-to-plasma concentration gradient, and at higher rates of flow by a maximum rate of transport ($T_m^cH_2O$) (4, 5). Several objections to these concepts were raised, not the least of which was the need for postulating an active water reabsorbing process in the collecting duct. Though several mechanisms for active water transport have been proposed (6-9), all present drawbacks in application to biological systems (10).

Wirz, Hargitay and Kuhn proposed an alternate mechanism for the concentration of the urine which did not depend on a process of active water reabsorption (11). Earlier observations by Ljungberg had established that the concentration of chloride in the kidney increases progressively from cortex to medullary papillae (12). By cryoscopic and micropuncture techniques Wirz and co-workers demonstrated a steady rise in the osmotic pressure of renal medullary tissue from the cortico-medullary boundary toward the papillary tip (11); under similar conditions, the fluid in the cortical tubules, distal as well as proximal, was consistently isotonic with serum. Furthermore, at any level within the medulla, no difference in osmotic concentration was discernible between tubular urine and capillary blood (12, 13). Observations by others have confirmed that in maximum hydropenia there is a progressive increase in solute concentration toward the apex of the medulla and that the final urine elaborated contains the same total solute concentration as the papillary tip (14-18). These observations suggested that the final concentration of the urine does occur in the collecting duct, but by passive equilibration of collecting duct fluid with the adjacent hypertonic interstitial fluid rather than by active transport of water.

The capacity of the kidney to establish a stratified, hypertonic medulla was

From the Section of Renal Diseases, the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

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* Postdoctoral Research Fellow, National Heart Institute, National Institutes of Health.

linked to the anatomic configuration of the loop of Henle. Several observers have emphasized the relation, in birds as well as mammals, between the development of the loop of Henle and the capacity to concentrate the urine (19-21). Hargitay, Kuhn and Wirz (11, 22) applied the concept of a countercurrent multiplier system to explain the progressive increase in solute concentration developed in the renal medulla. This system requires a small initiating concentration gradient which is readily achieved by sodium transport out of the water impermeable ascending loop of Henle. Since fluid at the tip of Henle's loop is hypertonic, the consistent hypotonicity of the fluid at the beginning of the distal tubule demonstrates a net loss of sodium from the ascending limb of the loop of Henle (16, 17, 23, 24). Moreover, the hairpin arrangement of the vasa recta enables these vessels to function as countercurrent "exchangers" so that solute diffusing from the efferent to the afferent limb is effectively trapped within the medulla (25-27).

According to this theory of urine concentration, during maximum hydropenia the amount of water passively abstracted from the collecting duct is determined by the osmotic gradient produced by the solute retained within the medullary interstitial fluid. The concepts of Smith and co-workers concerning the T^cH_2O curve produced by nonspecific solute diuretics* may be reappraised in the light of this additional insight into the renal concentrating operation.

Experiments in this laboratory have demonstrated that diuresis produced by organomercurials does not measurably change free water clearance (CH_2O) in hydrated man or T^cH_2O in hydropenic man, regardless of the levels of these parameters prior to the development of the diuresis (28, 29).† The administration of a nonspecific proximal diuretic during the mercurial diuresis generally augmented CH_2O or T^cH_2O . These data suggested that the saluresis produced by mercurials does not alter solute supply to the ascending limb of the loop of Henle. The contrast between the characteristics of mercurial diuresis, which does not appear to alter medullary solute supply, and diuresis produced by the nonspecific proximal agents permits an appraisal of the factors which define the T^cH_2O curve in man.

METHODS

All subjects were free of cardiovascular or renal disease. Maximum hydropenia was achieved by fasting for 16 hours prior to the study. In addition, the subjects received 0.5 ml pitressin tannate in oil intramuscularly 12 hours before the onset of the study and 200 mU/hr. of aqueous pitressin was infused throughout the study. Saline, mannitol and urea were infused at concentrations of 2.5 per cent, 10 per cent and 4 per cent, respectively. The mercurial agents were

* These include agents such as mannitol, salt, urea and aminophylline which inhibit proximal reabsorption of sodium and sweep more isotonic fluid into the loop of Henle.

† Free water clearance (CH_2O) = urine flow (V) - solute clearance (Cosm). Solute-free water reabsorption (T^cH_2O) = solute clearance (Cosm) - urine flow (V).

$$\text{Cosm} = \frac{U_{\text{osm}}V}{P_{\text{osm}}}$$

given intravenously in 3 ml doses after a steady state had been achieved at varying levels of solute excretion. To attain elevated levels of solute excretion mannitol was infused at a prescribed constant rate throughout the study. When glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured, priming doses of inulin and para-aminohippuric acid (PAH) were administered at

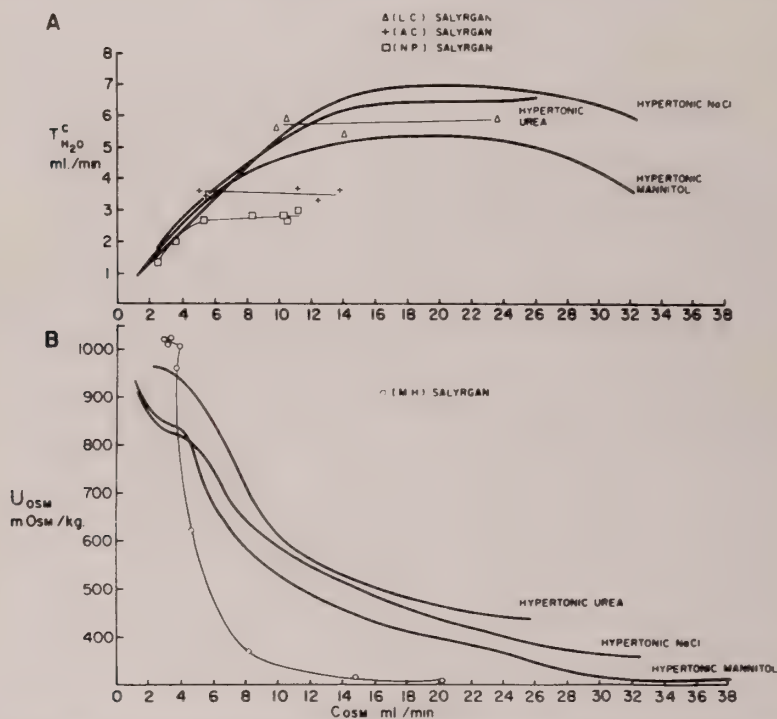


FIG. 1a. Effect of hypertonic NaCl, mannitol and urea infusions on solute excretion (C_{osm}) and free water reabsorption ($T^C_{H_2O}$). The curves are drawn from average values of 16, 9, and 12 experiments for NaCl, mannitol and urea, respectively. The lighter lines represent the data from 3 typical salyrgan experiments in which the mercurial was administered at different rates of control solute excretion.

FIG. 1b. Changes in urine osmolality (U_{osm}) and solute excretion (C_{osm}) during the diuresis produced by hypertonic NaCl, hypertonic mannitol, hypertonic urea, and a mercurial (salyrgan). Although the urea $T^C_{H_2O}$ curve is lower than the curve for salt, the level of urine osmolality appears higher since plasma osmolalities were consistently higher in the urea experiments.

the outset of the study and blood levels were then maintained by constant infusion. The precise protocols employed and laboratory methods used are detailed in a previous publication (29).

THE $T^C_{H_2O}$ CURVE

The typical changes in $T^C_{H_2O}$ and urine osmolality produced by the infusion of hypertonic salt or mannitol in hydropenic man are depicted in Fig. 1. As solute clearance (C_{osm}) increases, $T^C_{H_2O}$ rises sharply at first, then more gradually. As C_{osm} increases still further, $T^C_{H_2O}$ tends to level off and finally to de-

cline somewhat from peak values. For the purpose of exposition it is useful to divide this curve into four phases, although a sharp distinction between these segments cannot be made.

First Phase

The initial modest rise in solute clearance produced by a nonspecific solute diuretic is associated with a relatively small decline in urine osmolality (U_{osm}). Therefore, this small increment in solute clearance provokes a sharp rise in TCH_2O . When a mercurial is administered at a low control level of solute excretion, an abrupt increase in TCH_2O with the initial increase in solute clearance may also be noted (Fig. 1A, N.P.). Beyond this early rise, however, TCH_2O is constant for the remainder and more considerable part of the mercurial saluresis. TCH_2O remains constant throughout the diuresis when the mercurial is administered at higher control levels of solute excretion (Fig. 1A, A.C., L.C.).

Comment: It appears that this early sharp rise in TCH_2O , without appreciable change in medullary or urine osmolality, is due to presentation at the collecting duct of increased quantities of isosmotic fluid. In the baseline hydropenic state, extraction of a small amount of water from the meager volume of isotonic fluid in the collecting duct quickly brings the tubular fluid to the same concentration as the medullary interstitium, and water reabsorption ceases. As the quantity of isotonic fluid presented to the collecting duct increases, extraction of the same quantity of water results in tubular fluid less concentrated than before. Therefore, additional water is reabsorbed as long as medullary tonicity is preserved. The persistence of medullary tonicity suggests that this additional modest quantity of reabsorbed water can be effectively carried away by the vasa recta without appreciably reducing the total quantity of medullary solute.*

Second Phase

A. After the sharp initial rise, TCH_2O climbs more gradually as C_{osm} increases from approximately 4 to 14 ml/min. During this phase U_{osm} falls sharply and a divergence appears between the TCH_2O curve produced by hypertonic salt and that produced by hypertonic mannitol.

Comment: As the flow rate of isotonic fluid within the collecting duct increases, additional quantities of water are reabsorbed until the interstitium-collecting duct gradient is eliminated by the dissipation of medullary hypertonicity. For this reason, during this phase of the curve small increments in TCH_2O tend to produce relatively large falls in medullary concentration.

It seems reasonable to attribute the dissipation of medullary tonicity to a progressive washout of solute as additional water passes through the interstitial fluid. Such a mechanism would be consistent with reports that an osmotic

*Hulet and Smith have suggested that at the outset of a diuresis the diluting effect of a modest quantity of water entering the medulla (TCH_2O) permits further salt reabsorption from the loop of Henle, thus maintaining interstitial fluid concentration (30). Actually, in these experiments a slight fall in urine concentration does occur during this phase, but these data do not exclude their hypothesis.

diuresis reduces medullary solute content per gram of dry tissue (31, 32). The quantity of water necessary to effect this reduction in solute content depends in large part upon the rate at which solute is transported into the medulla via the loop of Henle. In the experiments with mercurials in which medullary solute supply presumably remains at control levels, dissipation of the medullary gradient occurs with back diffusion of relatively small quantities of water. Since the nonspecific diuretic agents present more solute to the ascending limb for transport to the medulla, progressively larger quantities of TCH_2O are necessary to eliminate the osmotic gradient. Higher levels of TCH_2O during a salt infusion than during a mannitol infusion are consistent with this explanation, because in the former instance larger quantities of absorbable solute per unit C_{osm} are presented to the loop of Henle.

B. When glomerular filtration rate (GFR) and renal plasma flow (RPF) are abruptly lowered during the course of a diuresis produced by a mercurial or by

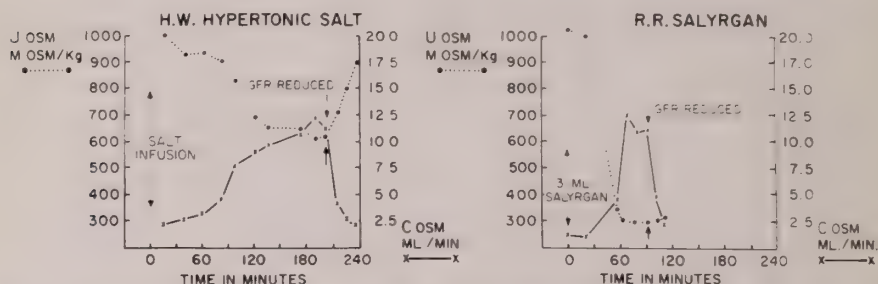


FIG. 2. Changes in urine osmolality (U_{osm}) and solute excretion (C_{osm}) produced by an experimental reduction in GFR during an organomercurial and a salt infusion diuresis. The arrows indicate the point where blood pressure was lowered by the intravenous administration of a ganglionic blocking agent (SC-1950).

hypertonic salt infusion, a prompt fall in C_{osm} and TCH_2O occurs (Fig. 2). In the experiment with the mercurial diuretic U_{osm} rises very little and TCH_2O is nearly extinguished. In the salt experiment U_{osm} rises appreciably, so that TCH_2O is the same at comparable levels of solute excretion whether during the development of the diuresis or after the reduction in glomerular filtration rate.

Comment: The importance of the solute supply to the loop is further emphasized by these experiments. Since the major increment in solute excretion after the administration of a mercurial diuretic presumably derives from a site distal to the loop of Henle, a decrease in glomerular filtration rate reduces the loop solute supply below control levels. The presentation of additional water to the collecting duct at this time is ineffective in raising TCH_2O since back diffusion of a small quantity of water may quickly carry away the reduced quantity of medullary solute present. As a result, U_{osm} and TCH_2O are lower than at comparable levels of solute excretion during the development of the diuresis. During the salt diuresis, at any rate of collecting duct flow, the same amount of salt will reach the ascending limb of Henle's loop, whether the diuresis is developing or has been curtailed by the drop in GFR. Accordingly, the U_{osm} and TCH_2O are the same at corresponding rates of C_{osm} on both limbs of the curve.

Third Phase

Between a Cosm of 14 and 25 ml min., the $T^{\circ}H_2O$ values tend to stabilize. The peak values attained with salt as the infusing solute are somewhat higher than those obtained with mannitol.

Comment: This portion of the $T^{\circ}H_2O$ curve with nonspecific diuretics is suggestive of the action of a mercurial diuretic since $T^{\circ}H_2O$ remains constant as Cosm increases considerably. A stable level of $T^{\circ}H_2O$ appears to develop when solute transfer at the loop becomes relatively fixed and the flow rate in the collecting duct provides a quantity of water for back diffusion sufficient to dissipate medullary tonicity. The constant rate of medullary solute supply during mercurial diuresis can be explained by the assumption that no additional solute is arriving at the loop. It is more difficult to explain a relative constancy of solute supply to the medulla during progressive mannitol or salt diuresis. It may be that sodium transport has reached a maximum, either because of the markedly increased rate of loop flow (30), or because of saturation of the active loop transport mechanism (T_m loop Na). If the latter is the limiting factor, it is surprising that higher maximum levels of $T^{\circ}H_2O$ are achieved with salt than with mannitol.

When $T^{\circ}H_2O$ is relatively stable, urine osmolality progressively falls as the quantity of isosmotic fluid reaching the collecting duct increases. It might be anticipated that a gradient for water diffusion between the collecting duct and medullary interstitium would thus persist, causing a measurable rise in $T^{\circ}H_2O$. However, during this phase of the curve medullary tonicity is so easily dissipated by any further increase in back diffusion of water that a minimal change in this quantity might not be detectable.

It has been suggested that because of the rapid flow rate distal tubular fluid fails to reattain isotonicity, so that solute-free water is extracted from the collecting duct without apparent change in the calculated $T^{\circ}H_2O$ (18, 27). However, micropuncture experiments in the hydropenic hamster and rat have demonstrated that late distal tubular fluid is isotonic even at flow rates eighty times greater than the control flow rate (17). Furthermore, this argument is not compatible with the observation that salt diuresis produces a higher maximum $T^{\circ}H_2O$ and a less conspicuous fall-off (fourth phase) than mannitol. With salt rather than mannitol as the major solute in the distal tubule, the degree of early distal tubular hypotonicity has been shown to be more pronounced (17, 33). It would therefore be anticipated that the depressant effect on the $T^{\circ}H_2O$ curve would be more evident during a salt diuresis. Moreover, with solute diuresis in man approaching 40 ml min., urine hypotonicity is rarely, if ever, observed.*

Fourth Phase

Beyond a Cosm of 25 ml min., $T^{\circ}H_2O$ falls slightly with salt as the loading solute and somewhat more with mannitol. If a comparable or higher level of solute excretion is produced by administering a nonspecific solute diuretic during a mercurial diuresis, $T^{\circ}H_2O$ generally increases (29).

* This finding is in distinct contrast to that in the dog, in which a more modest solute diuresis provokes the formation of a dilute urine (18). These considerations may therefore not be applicable to the dog.

Comment: The decline in $T^{\circ}H_2O$, also noted by Raisz *et al.*, implies that with a further increase in the rate of flow through the loop of Henle, solute transport at the ascending limb may fall below maximum (34). * The more marked fall during mannitol infusion, in which sodium must be transported from a much lower intratubular concentration than during salt diuresis, would be consistent with this explanation.

The hypothesis that distal tubular fluid fails to regain isotonicity is again countered by the arguments previously stated. Failure of collecting duct fluid to achieve equilibrium with the interstitium at very high flow rates offers another possible explanation, but this alternative is weakened by the demonstration that at very high rates of flow $T^{\circ}H_2O$ may be increased by the superimposition of a nonspecific solute diuretic on a pre-existing mercurial diuresis.

Urea

A hypertonic urea infusion produces a $T^{\circ}H_2O$ curve very similar to that produced by mannitol, except that $T^{\circ}H_2O$ values stabilize at slightly higher levels.

Comment: The enhanced urinary concentration observed with high protein diets or urea infusions in man and other species has been previously reported (18, 34-40). Since the influence of urea and mannitol on salt reabsorption in the proximal tubule is similar, it might be anticipated that the $T^{\circ}H_2O$ curve obtained with urea would coincide with that produced by mannitol. The observed difference between these two curves suggests that in the former instance urea provides an additional source of medullary solute throughout the diuresis. Micropuncture studies have demonstrated that the quantity of urea entering the distal tubule exceeds that entering the loop of Henle (41). Thus, it would appear that the medullary urea derives primarily from the collecting duct.

The observation that the $T^{\circ}H_2O$ curves reach a plateau at the same rate of solute clearance with either mannitol or urea infusions suggests that the entrance of urea into the medulla depends in part upon the deposition of salt therein (27). In this view the abstraction of collecting duct water establishes a favorable gradient for the passive back diffusion of urea (18, 27, 40). However, on the basis of such indirect evidence, it is not possible to exclude some active urea transport, as demonstrated in other species (42, 43).

Medullary Blood Flow

Induction of a pyrogen reaction during the course of a mannitol diuresis causes a considerable increase in effective renal plasma flow without appreciably changing the glomerular filtration rate (Fig. 3). In association with this hemodynamic alteration, $T^{\circ}H_2O$ drops sharply.

Comment: These observations, as well as those reported by Brandt *et al.*, em-

* Alternatively, the characteristics of the third and fourth phase of the $T^{\circ}H_2O$ curve may be attributed to a progressive medullary hyperemia developing during the diuresis. Such a change could explain the plateau or fall in retained medullary solute despite a constant or increasing rate of loop sodium transport. The increased rate of medullary blood flow might result as a nonspecific consequence of proximal diuresis.

phasize the role of the unique circulation within the medulla in maintaining the countercurrent operation (44). It is probable that an increase in renal plasma flow enhances medullary blood flow. An increase in the latter would reduce the efficiency of the countercurrent exchanger in accordance with the calculations of Hargitay and Kuhn (22). This would in turn limit the trapping of solute in the medulla, dissipate the prevailing osmotic gradient, and reduce the $T^C H_2O$.

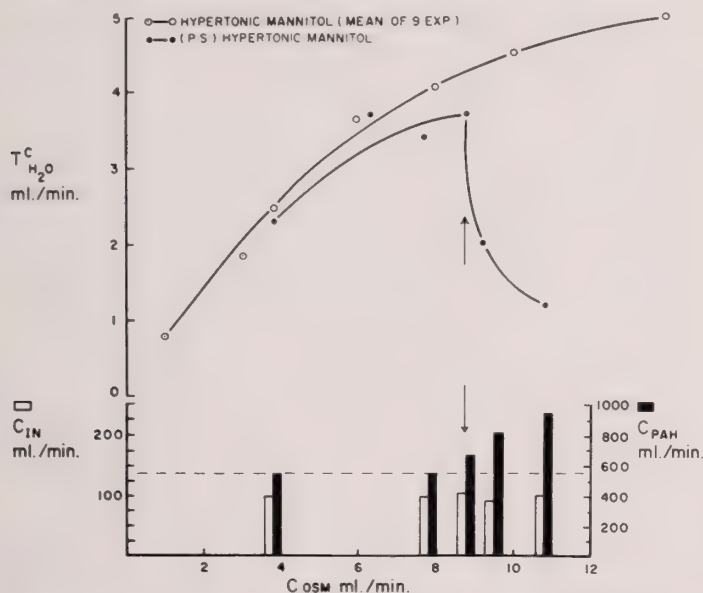


FIG. 3. Effect of a pyrogen reaction on free water reabsorption ($T^C H_2O$) during a hypertonic mannitol diuresis. The arrow indicates the point at which the pyrogen reaction began. The normal curve produced by hypertonic mannitol is included for comparison.

CONCLUSION

The foregoing hypotheses presented to explain the $T^C H_2O$ curve produced by varied diuretic techniques remain tentative, but they provide a framework for further experimental confirmation and a basis for analysis of numerous clinical states characterized by an inappropriate concentration of the urine. Experimental evidence interpreted in these terms has suggested that changes in the medullary circulation may explain the hyposthenuria noted in sickle cell disease (45) and has yielded insight into the concentrating defect associated with potassium depletion (46). In the persistent hyposthenuria of bilateral pyelonephritis relative medullary hyperemia may prove important (47). The persistence of urinary concentration in syndromes in which renal flow is reduced by extra-renal processes may also find explanation in this type of analysis (48).

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COMBINATION CHEMOTHERAPY OF ADVANCED OVARIAN CARCINOMA WITH THE ANTIMETABOLITE, METHOTREXATE, AND THE ALKYLATING AGENT, THIOTEPA

EZRA M. GREENSPAN, M.D., AND MACK FIEBER, M.D.

New York, N. Y.

INTRODUCTION

The standard treatment of ovarian carcinoma until recently has consisted of excisional surgery, whenever feasible, followed by a course of radiation for residual or recurrent pelvic disease (1, 2). In selected patients, radioactive gold has been administered intraperitoneally for the control of ascites (3). The relatively long survival of a small minority of patients so treated, as well as the spectacularly rare instances of spontaneous remission, have served to obscure the usually relentless progression of disease in most victims of this common neoplasm. The overall five year survival rates after surgery remain at 10 to 35 per cent, with little or no indication of recent improvement (4). The two year survival approximates only fifty per cent among the unselected cases comprising all clinical stages of disease.

The clinician, confronted with the symptomatic management of advanced ovarian carcinoma (Stage III and IV), must attempt to ameliorate the progressive course of four to six months of intractable abdominal pain, peritoneal and pleural effusions, and terminal episodes of intestinal obstruction. Because of the presence of bulky, easily observable tumor masses, ascites, and a relatively short survival, the patient with Stage III or IV ovarian neoplasm (classification of Walter (1) or Keetal (3)) represents an excellent subject for investigation of the newer chemotherapeutic agents. An accurate objective response index based on gross tumor regression is possible in Stage IV patients previously receiving only a simple open biopsy or aspiration biopsy for diffuse pelvic and upper abdominal multinodular disease. Any major effect of chemotherapy on survival should be discernible, since less than ten per cent of an average group of untreated Stage IV patients survive more than one year (1, 2, 4, 5), and less than three per cent survive more than 18 months (4).

The comparative appraisal of chemotherapy for ovarian carcinoma requires accurate matching of both the clinical stage of disease and the past treatment in each case. Although the reduction of tumor masses in recurrent Stage III disease (gross metastases above the pelvis recurrent after oophorectomy and/or radiotherapy) is as easy to detect as in Stage IV patients (previously untreated upper abdominal disease), both the survival and likelihood of tumor shrinkage is less predictable in the Stage III patient than in the Stage IV patient. The one year survival rate in Stage III varies widely and may exceed 40 per cent (4).

From the Department of Medicine and the Tumor Chemotherapy Clinic, The Mount Sinai Hospital, New York, N. Y.

compared to the much shorter survival of Stage IV patients. A longer survival of Stage III patients could reflect an originally slower growing neoplasm, the fortuitous detection of disease at an earlier stage of recurrence, the favorable influence of bilateral oophorectomy, or the efficacy of pelvic radiotherapy. A smaller volume of suprapelvic metastases in Stage III compared to Stage IV could also account for a slower advent of terminal intestinal obstruction. A shorter survival of Stage III disease could be related to biological resistance in chronologically old disease. Because of these uncertainties, the patient with untreated potentially less resistant Stage IV disease, rather than the more variable chronologically older recurrent Stage III disease, offers the most valid test of the action of chemotherapy on tumor regression and survival.

The results of intraperitoneal radioactive gold (Au^{198}) therapy since 1951 have provided a useful parameter of clinical palliation in a selected group of Stage III or IV cases with massive thin ascitic fluid. Control of ascites and associated clinical symptoms may be obtained for two or three months in from one-third to one-half of patients in this selected group (3). Usually, little or no regression of large solid multinodular tumor masses occurs after radioactive gold, since its short beta ray path (2 mm) penetrates only thin peritoneal implants. Extensive clinical trials of deep supervoltage x-ray therapy have also resulted in data with which to compare chemotherapeutic methods of treatment for the advanced case of ovarian carcinoma (1, 2, 4). Although definite prolongation of life has been demonstrated in x-ray treated neoplasms which are confined to the pelvis (Stage II = incompletely removed at time of surgery; Stage III = recurrent after surgery), the effect of x-ray on the diffuse Stage IV patient has been disappointing (1, 2, 4). This is best exemplified by a recent report by Weed from the Ochsner Clinic (6) in which not a single one year survivor was obtained among 41 cases with inoperable or incompletely removed tumors regardless of whether postoperative therapy consisted of deep radiotherapy or radiogold. This extremely low percentage of one year survivors in Stage IV cases has been confirmed in other series (2).

The potential value of alkylating agents in systemic chemotherapy of ovarian carcinoma was first demonstrated in 1952, when Rundles and Barton (7) noted the favorable effects of oral triethylene melamine (TEM) and Seligman *et al.* (8) observed short-term palliation after intravenous hemisulfur mustard (2-chloro-2-hydroxydiethylsulfide). Sykes and others in 1956 reported eight cases of objective tumor regression and 14 temporary symptomatic responses among a total of 26 patients treated with TEM (9). Noteworthy was the observation that the response to hemisulfur mustard was as good if not better by the intravenous route than by intraperitoneal administration. Hemisulfur mustard induced transient relief of ascites and short-term symptomatic responses in 9 of 14 of Rutenberg's (10) patients and in 21 of 30 patients treated by Green (11). Reduction of tumor masses occurred in 8 of 30 of Green's cases. Despite these encouraging results, further use of those earlier alkylating agents (10, 12) was discouraged by their serious toxicity, viz., severe neurotoxicity (HSM), and unpredictable hematopoietic depression (TEM).

Clinical studies (12-15) have been directed more recently towards the long-acting alkylating agents, Thiotepe (thiophosphoramidate), and Chlorambucil (Leukeran), effective by intramuscular and oral routes respectively. Approximately similar rates of response to the various alkylating agents have led some observers to the conclusion that there is probably no single preferred alkylating agent (16).

An additive or synergistic therapeutic effect exerted by two antineoplastic agents acting by different mechanisms, viz. an alkylating agent and an anti-metabolite (antifol) has been demonstrated experimentally by us (17) and others (18) in 1951 and 52. In synergistic combinations, the net toxicity from two individually toxic drugs given at adequately therapeutic dose levels, is not additive to the host, whereas enhanced therapeutic results may be obtained in survival and tumor regression indices. Conclusive evidence of synergism at the clinical level has been established, thus far, only in children with acute leukemia treated with combinations of Methotrexate, 6-Mercaptopurine, and steroids (19). Suggestively favorable results have been recently reported with combinations of antifols, alkylating agents, and actinomycin in males with choriocarcinoma (20, 21).

In a preliminary clinical study of Methotrexate in a variety of solid tumors, one of us (E.M.G.) failed to observe any inhibitory effect in four cases of mucous-cell adenocarcinoma of the ovary (22). The possibility that folic acid antagonists might exert an antitumor effect in patients with ovarian carcinoma seemed remote until a case of papillary serous cystadenocarcinoma metastatic to the lung (V.I.) was observed to show objective tumor regression after Methotrexate therapy alone. This stimulated study of the combined effect of the folic acid antagonist, Methotrexate, in conjunction with the alkylating agent, Thiotepe, in far-advanced ovarian carcinoma. Among our group of 35 patients treated with this combination of agents, about two-thirds (23 Stage IV cases) received no previous radiation therapy, radiogold, or extirpative surgery. It was hoped that by treating these advanced cases solely with combination chemotherapy, a more precise opinion might be obtained of the chemotherapeutic potential *per se*, in terms of: a) incidence of initial regression of tumor; b) duration of sustained clinical remission on maintenance therapy; and c) response, if any, to other agents, in particular to the alkylating agent (Cytosan), after development of complete resistance to maximal dosage of the antifol-alkylating agent combination.

PROCEDURE

Chemotherapy was the sole method of treatment in 35 patients with ovarian carcinoma followed for periods of 10 days to 2½ years. Twenty-eight patients had begun treatment more than one and one-half years before presenting this report. Thirty of these patients were hospitalized at The Mount Sinai Hospital on the private or ward services. Combination treatment in Stage IV cases was instituted as early as two days after abdominal laparotomy, but usually at the end of the first postoperative week. A priming dosage of Thiotepe, consisting of

45 to 60 mg was administered intramuscularly over a period of three to eight days. An individual oral daily dose of Methotrexate was calculated on the basis of a weekly aggregate dosage per course varying from 0.75 to 1.5 mg per kg (50 to 125 mg total dose). The lower aggregate dosage range was employed for poor-risk patients with evidence of azotemia, fever, cachexia, diarrhea, severe anemia prior to treatment, or history of massive radiation. Patients with previous history of gastrointestinal bleeding were not accepted for treatment with the antifols. Methotrexate was administered each morning, usually for a 7 day period, but only after the patient had been examined for signs of impending antifol toxicity. The development of a stomatitis was the first reliable sign of the folic acid deficiency state in the patients receiving the combination. Stomatitis usually preceded leukopenia, as noted previously in solid tumor patients (23). The aim was to gradually induce the toxic-deficiency state so that the upper gastrointestinal tract symptoms would signal the need for stopping the drug before severe depressive effects could occur in the hematopoietic system. In every case, the daily dose, ranging from 7.5 mg to 15 mg was administered for five days or longer until definite signs of stomatitis appeared. These usually consisted of burning mouth, or the development of flat, white, atrophic areas of epithelium on the buccal mucosa, tongue, or lips. The Methotrexate was promptly discontinued as soon as these signs appeared. This toxic-deficiency state usually became more intense on the second or third day after withdrawal of medication. Anorexia usually appeared and, in some instances, was accompanied by nausea, crampy abdominal pain, vomiting, low-grade fever, and rash. Although recovery was usually apparent within five to seven days after withdrawal of Methotrexate, the second course of Methotrexate was withheld until the third or fourth week after commencing the initial Thiotepe-Methotrexate combination. If clinical regression had been induced by the combination therapy, and the patient had subsequently shown an improved nutritional status, the aggregate weekly dosage of the second course of Methotrexate was increased 20 to 25 per cent. Tolerance to Methotrexate therapy after remission was usually better than during the initial course of the antifol combination. Maintenance Thiotepe was resumed in the third week after the initial treatment at a dose of 15 mg I.M., once per week. If no leukopenia had been induced during the third week small increases in the weekly Thiotepe dosage was given. The aim was to maintain a constant leukopenia between 3,000 to 4,000 white blood cells per cu mm. After several months, it was often sufficient to give Thiotepe at 10 to 21 day intervals. Conclusions regarding the efficacy of the chemotherapy combination were held in abeyance until the patient had received a minimum of two courses of Methotrexate together with the necessary amount of Thiotepe to maintain a modest leukopenia over a four to six week period. The classification of response was essentially that followed by Masterson (15) and Coonrad (12).

The Thiotepe was maintained in patients who had responded until the first evidences of recurrence were observed. Then, another course of Methotrexate was administered with some increase in the Thiotepe dosage. If no response was noted, the disease was designated as "combination resistant." Cytosan was then

administered at a time when the patient appeared to be approaching a terminal state.

MATERIAL

The preponderance of advanced disease in this series was evident since there were 23 Stage IV cases, compared to 9 Stage III cases, and 3 Stage II cases among the total of 35 patients treated with combination chemotherapy. None of the Stage IV cases had received radiotherapy. In only two of the 23 Stage IV cases, the surgeon performed a bilateral salpingo-oophorectomy by cutting through pelvic tumor despite diffuse upper abdominal disease. Thus, the ovaries remained *in situ* in 21 cases who were treated by chemotherapy exclusively. Surgical intervention had consisted of a simple open biopsy of intra-abdominal (usually omental) disease in 18 cases, with the coincident removal of whatever amounts of peritoneal fluid were released during the laparotomy procedure. Three patients had received only a diagnostic peritoneal aspiration. Twenty patients had ascites in association with many upper abdominal metastases. Paracentesis was not performed postoperatively during the first month of combination chemotherapy except in the totally unresponsive patients. Paracentesis was not necessary in the responders until the "combination resistant" stage was reached. There were nine Stage III patients with advanced pelvic disease recurrent after surgery and/or radiation given at least four months previously. Three Stage II patients were treated within two weeks after operation at which time known residual, but externally nonpalpable disease remained in the pelvis. Oophorectomy had thus been performed in all 12 patients with Stage II and Stage III disease. The pathological diagnoses will be alluded to below.

RESULTS

Thirty-two of the total of 35 patients were able to complete the course of combination chemotherapy consisting of priming and maintenance doses of Thiotepe, in conjunction with the two courses of Methotrexate, three to six weeks apart. Objective tumor regression with partial or complete clinical remissions were obtained in 21 of the 30 Stage III or IV patients treated for two weeks or longer (Table I). Nineteen of the 21 favorable responses occurred among the 23 patients in whom the pathological diagnosis was serous cystadenocarcinoma (papillary, solid, or mixed types). The excellent and good remissions were obtained only in patients with this pathologic lesion. Excellent results occurred in two patients with psammoma body calcifications. Two fair responses occurred in patients with anaplastic ovarian carcinoma. No responses were observed in five patients with mucus-cell adenocarcinoma, one case of anaplastic carcinoma, one case of pseudomucinous cystadenocarcinoma, and in one patient with a malignant Brenner cell tumor.

Since 13 excellent results and six good responses were obtained among the 32 symptomatic Grade III and IV cases (Table I), a worthwhile clinical palliation was achieved in at least half of the patients treated. These excellent remissions consisted of total regression of all palpable masses, pleural effusions, and ascites.

associated with a return to a normal living routine for a minimum of three months. Eleven of the excellent results were obtained with an initial simultaneous combination of Thiotepa and Methotrexate. The other two excellent responses occurred in our earliest cases in this study, in which a rapid but incomplete regression of tumor had been initiated by Thiotepa alone. Recurrence

TABLE I
Ovarian Carcinoma—Stages III & IV

Results	Papillary Cystadenocarcinoma	Others
Excellent	13	0
Good	6	0
Fair	0	2
Equivocal	1	0
Failures	0	8
Toxic Death	2	0
Total	22	10

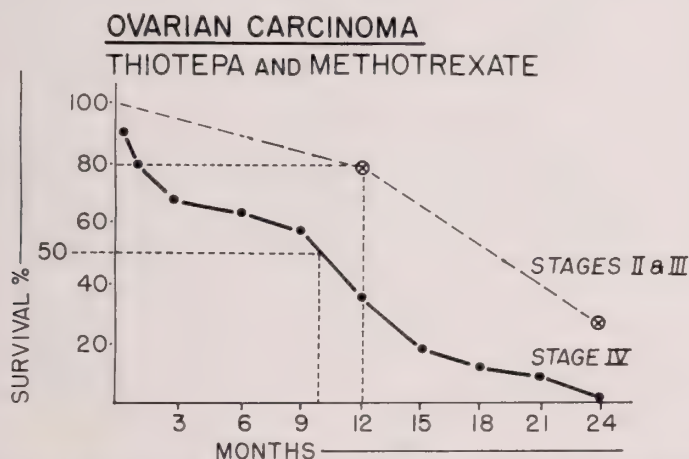


FIG. 1. Survival after combination chemotherapy in 23 Stage IV patients contrasted with 10 Stage II or Stage III patients.

of ascites and renewed tumor growth, which became apparent within five weeks after the Thiotepa alone, responded completely in these two cases when Methotrexate was added and given to the point of induced stomatitis.

The average duration of the nine excellent responses in Stage IV disease was 6.9 months prior to relapse. The longest complete regression in this group has continued for nineteen months, thus far without any signs of recurrence. The survival of all 23 Stage IV cases, (only two still living), since starting combination chemotherapy, is shown in Fig. 1. Only 7 of these 23 Stage IV cases survived more than one year. Of these, four died between 12 to 15 months after treatment;

one is asymptomatic and clinically free of disease for 19 months. Two of these patients died, 23 and 24 months after beginning therapy. Survival in the nine excellent Stage IV responders averaged 9.2 months. The six good, and two fair responses were associated with a partial regression of tumor masses, ascites, and pleural effusions, together with marked improvement in symptoms and performance. The duration of the six good responses varied from three to ten months. The two fair responses were of less than two months duration. There was one equivocal result, eight failures, and two toxic deaths (Table I).

The excellent responses in Stage III patients were associated in three of four instances with survival of more than one year, and control of palpable disease for from 11 months up to 24 months. The fourth patient obtained an excellent remission, but stopped maintenance chemotherapy to return to her native land. She died five months after the initial response, and three months after stopping chemotherapy.

Apparent control of incompletely removed pelvic disease for more than one year was obtained in each of the three Stage II patients treated with Methotrexate and maintenance Thiotepe. It was noted that 8 of the 10 patients with Stage II or III disease who continued maintenance treatment with chemotherapy were surviving at the time of this report for more than one year after onset of therapy. All of these patients with Stage II and Stage III disease had been subjected to bilateral oophorectomy, in contrast to the Stage IV group.

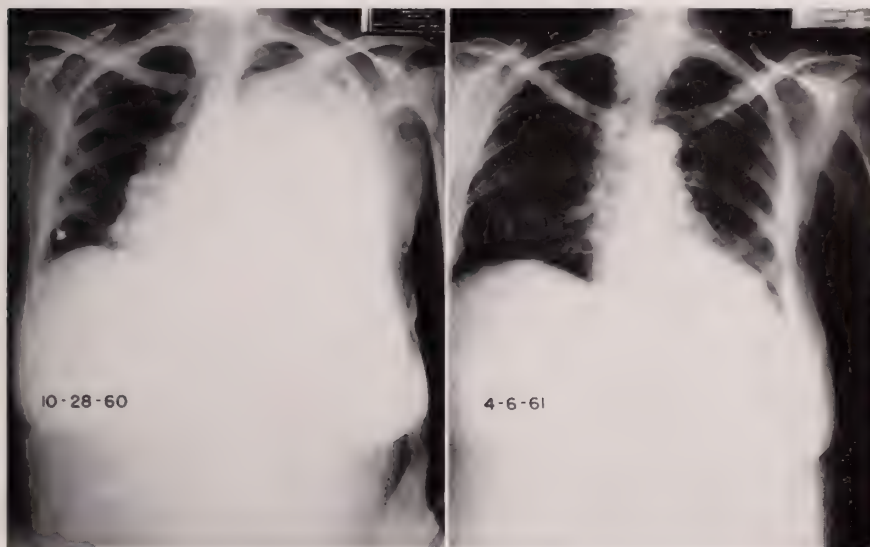
RESPONSE OF SEROUS EFFUSIONS

Some degree of ascites was present in 20 of the 32 Stage III or IV patients. Massive ascites was the conspicuous physical feature in 11 patients. Subsidence of ascites was induced by the chemotherapy in 12 patients. In nine cases, ascites was totally suppressed for six months or longer. Resolution of ascites in some patients was observed in as little as two weeks after starting chemotherapy. Ultimate, but slow resolution in ascites occurred in two patients with diffuse peritoneal psammoma body calcifications. In one of these patients, resolution of ascites was also associated with the slow, but essentially complete disappearance of massive pleural effusion after five months (Fig. 2, 3). Four other cases of pleural effusion showed more rapid responses.

TOXICITY

Satisfactory tolerance to the Thiotepe-Methotrexate therapy was observed in 32 of the 35 patients treated. Severe toxicity occurred in three cases. Although two of these patients were in a terminal state when treatment was begun, the severe toxicity was nevertheless unexpected, and contributed to their demise. Death occurred ten and twelve days, respectively, after commencing the drugs despite use of citrovorum factor intravenously (citrovorum factor is ineffectual once a severe toxic state is established as a result of complete irreversible enzyme blockade). Prior to therapy, one of these patients suffered from a chronic diarrhea with a malabsorption syndrome due to massive abdominal metastases;

the other had received two courses of supravoltage x-ray therapy through very large abdominal ports, four months before the combination therapy. These patients apparently had unusually low endogenous reserves of folic acid metabolites. In retrospect, a lower dosage and a more gradual induction of antifol toxicity might have been tolerated satisfactorily by these poor-risk patients. In a third case, a marked reduction in antifol dosage permitted recovery from severe, but not unexpected toxicity in an emaciated 77 pound female who was suffering from active regional ileitis, together with disseminated ovarian carcinoma. She obtained a good short-term remission after recovery from toxicity.



FIGS. 2 and 3. Slow progressive resolution of pleural effusion in patient with massive ascites and diffuse abdominal tumors from papillary serous cystadenocarcinoma with psammoma bodies. Treatment was exclusively with combination chemotherapy.

but, upon subsequent treatment with antifols six weeks later, her tolerance was still demonstrably poor.

The toxicity from the combination was relatively well tolerated and essentially predictable in all cases except the three above-mentioned patients. Minimal stomatitis was purposely induced in all patients by the Methotrexate. Leukopenia was induced in all patients in from three to six weeks after starting the combination. Troublesome clinical bleeding syndromes (gastrointestinal bleeding) developed in only one patient among the 35 patients, almost all of whom had massive intra-abdominal disease. Mild subcutaneous ecchymosis was induced in three patients with prompt subsidence upon cessation of the Methotrexate. Pyogenic cutaneous infection (i.e. furunculosis, paronychia) developed as a secondary effect of the chemotherapy in four patients, but was easily controlled with antibiotics. Vaginitis associated with a transient dermatitis at the height of the antifol stomatitis was troublesome in two patients, but responded readily to emollients.

EFFECT OF CYTOXAN IN "COMBINATION-RESISTANT" DISEASE

Ten patients were given Cytoxan orally or intravenously after the development of recurrent and apparently terminal disease, resistant to the combination. Eight were treated for a minimum of two weeks or longer with a dose of 2 Gm or more. Some degree of shrinkage of tumor masses was observed in six of these eight patients when a profound drop in the white count occurred associated with alopecia. In four, marked regression of masses occurred (i.e., Cases 1, 3), but was associated with fever, profound leukopenia, pancytopenia, and bleeding. Only one patient developed a worthwhile partial clinical remission (Case 3) after Cytoxan therapy. In addition, a patient with a huge malignant Brenner cell tumor showed a partial regression and response for 1½ years on intermittent Cytoxan therapy, after failure to respond to the adequate doses of the Thiotepe-Methotrexate combination.

Patient #1

L. H., a 52 year old female presented with massive abdominal swelling due to an extensive Stage IV carcinoma with moderate ascites and many metastases in the upper and midabdomen, the omentum and both lumbar gutters. Biopsy from an omental nodule showed papillary serous cystadenocarcinoma of the ovary.

On the third postoperative day, the patient was started on a priming course of 60 mg of Thiotepe, 15 mg per day I.M., in conjunction with oral Methotrexate therapy at a dosage of 10 mg per day. On the seventh day of antifol therapy the first sign of oral stomatitis appeared, necessitating prompt withdrawal of the Methotrexate. The lowest leukocyte count reached after two weeks was 4,850 cm. The patient was discharged for routine convalescence. Maintenance Thiotepe therapy was begun on the third postoperative week at a dose of 15 mg per week. Progressive diminution in all palpable tumor masses and pelvic tumor masses was observed during the third and fourth postoperative weeks. The second course of Methotrexate to the point of minimal stomatitis was given ambulatory at a dosage of 10 mg per day for seven days during the second postoperative month.

The interval between maintenance Thiotepe injections was gradually prolonged to 15 mg every second week as a leukopenia of 3,000 to 4,000 was attained. The patient enjoyed a complete clinical and total objective remission for six and one half months.

At the end of the seventh postoperative month, an ill-defined left parametrial mass was first noted in association with development of abdominal pain. A third course of Methotrexate was given, and the Thiotepe was increased to the point of thrombopenia with platelet counts between 80,000 and 100,000 cm and leukopenia of 2,800 leukocytes cm. There was no evidence of clinical bleeding.

Despite this intensified chemotherapy, aggressive nodular tumor regrowth continued in the seventh and eighth postoperative months. A fourth course of Methotrexate was given to no avail, whereupon the combination of Thiotepe and Methotrexate was stopped. Signs of subacute intestinal obstruction appeared. A trial of Cyclophosphamide (Cytoxan), 150 mg by mouth, each day was begun. This was increased to 200 mg per day after one week, with only minimal nausea. Maximum leukopenia to 350 leukocytes cm occurred 12 to 14 days after increasing the Cytoxan dosage, and was associated with the development of persistent nausea, fever and vomiting. Definite diffuse alopecia appeared. Intravenous fluid therapy, antibiotics, and small doses of steroids were given with some clinical improvement for several weeks, associated with definite softening and regression of palpable tumor masses, but with persistence of fever. The leukopenia returned to the 2,500 to 3,500 per cm level within ten days after withdrawal of Cytoxan. Then severe right lower quadrant abdominal pain suddenly developed, accompanied by signs of peritonitis and shock.

The patient expired 18 hours after the onset of this acute episode, diagnosed as "bowel

perforation." Autopsy performed ten months after the original surgery showed fecal peritonitis secondary to four discrete small perforations along the mesenteric aspect of the small bowel in several bowel loops adherent low in the right side of the pelvis. A small neoplasm was found in the left ovary. Intramural carcinoma cells were seen with marked necrosis, tumor giant cells and areas of adenomatous differentiation. Residual carcinoma was encountered microscopically in the right ovary. There were no hepatic or extra-abdominal metastases.

Patient #2

H. B., a 41 year old female was found at laparotomy on April 1, 1960, to have numerous intra-abdominal, omental, mesenteric, and pelvic nodular metastases. A somewhat larger mass was found to be filling the pelvis extending from the left ovary. A small amount of free abdominal fluid was noted. Bilateral salpingo-oophorectomy was performed by cutting across tumor tissue. A diagnosis of "papillary serous cystadenocarcinoma grade II" was made by Dr. S. Otani.

Postoperatively, the hard cul-de-sac mass remained. On the third postoperative day, the patient was started on a priming course of 60 mg of Thiotepe (see Case #1), in conjunction with 10 mg of Methotrexate orally each day. On the eighth day of therapy, when minimal stomatitis first appeared the Methotrexate was stopped. By the tenth day, several painful, flat, white, atrophic ulcerations were noted in the buccal mucosa and posterior wall of the pharynx, associated with some dysphasia, slight nausea, and abdominal cramping pain. At this time, the white blood count was 5,700 cm and the platelets, 180,000 cm.

In the third postoperative week, maintenance Thiotepe was instituted: 15 mg once per week. The patient's upper and midabdomen gradually returned to normal contour by the fourth week of therapy at which time a softened, almost fluctuant, tender mass in the cul-de-sac could be palpated.

During the fifth week after initiating chemotherapy, the patient noted a sudden development of tenderness and swelling in the pelvic and suprapubic regions accompanied by low-grade fever and signs of peritoneal irritation. Antibiotics and a second course of Methotrexate were instituted at doses of 10 mg by mouth. Eleven days after starting the Methotrexate therapy, the minimal oral mouth lesions appeared, necessitating withdrawal of further antifol medication.

All signs of fluid and the pelvic mass disappeared within two weeks thereafter. The patient resumed normal activity which has persisted during nineteen months of observation without any clinical evidence of carcinoma. Three additional courses of Methotrexate have been given, ambulatory, while maintaining Thiotepe at dosage sufficient to produce moderate leukopenia of 3,000 to 4,000 cm. Platelets have remained above 80,000 cm, without purpura. Hair growth has been normal and appetite, weight, stamina, libido and bowel function entirely within normal limits.

Patient #3

B. K., a 46 year old female was operated upon in March, 1959, for multinodular tumor masses extending above the pelvic brim. At operation, the ovaries, removed by cutting across tumor tissue, showed bilateral serous adenocarcinoma with solid, medullary, and papillary features. The same histologic lesion was found in several removed omental nodules. A priming dose of Thiotepe, consisting of 15 mg every 48 hours for four doses, was begun on the fourth postoperative day, plus Methotrexate therapy, 15 mg each day by mouth for six days.

The first signs of induced stomatitis developed on the sixth day of antifol therapy. Rapid disappearance of all palpable evidence of abdominal and pelvic disease occurred between the 10th to 20th postoperative days. Weekly injections of 15 mg of Thiotepe were begun three weeks postoperatively, and three additional courses of Methotrexate were given at intervals of three weeks, through June 1959. On each occasion, the Methotrexate was stopped at the first sign of stomatitis. The combination therapy was well tolerated with only minimal transient anorexia, and no nausea, vomiting, alopecia or purpura.

Because the patient moved in August to a small town distant from New York, therapy was changed to the oral alkylating agent Leukeran instead of the intermittent intramuscular Thiotepe. Leukeran (Chlorambucil), 8 mg per day was given while the patient continued in complete clinical remission. Seven months postoperatively, in November 1959, the first palpable recurrent mass was noted high in the lumbar gutter. An increase of Leukeran to 10 mg per day for three weeks, together with a fifth course of Methotrexate, resulted in regression of this left flank mass. Continuous Leukeran and two additional courses of intermittent Methotrexate were administered for another eight months, until June 1960, when a persistent suprapubic pelvic recurrence developed. Therapy was changed to a combination of Thiotepe and Methotrexate, and dosage was increased to the point of marked leukopenia (1,900/cm) and thrombopenia (60,000 platelets/cm). A mild purpura appeared coincident with the regression of the suprapubic mass. Chemotherapy was withheld for one month to allow recovery from thrombopenic purpura. In August, 1960, Leukeran was resumed at 8 mg per day, with the hope that the depressive effect on platelets would be less than with the Thiotepe. However, recurrence of gross palpable disease was noted again in September.

Since the patient appeared to be approaching a resistant stage with the Thiotepe, Leukeran, and Methotrexate therapy, Cytoxan therapy was given. Dosage of 150 mg per day for two weeks resulted in a maximum leukopenia of 2,950 cm, but the hemoglobin was maintained and no further purpura occurred.

Partial shrinkage with softening of the tumor mass was obtained with Cytoxan therapy, but complete regression was never again observed. Gradual massive recurrence with severe pressure effects on the bladder developed in January, 1961, despite additional Methotrexate and increasing doses of Cytoxan. A course of Cobalt therapy directed at the pelvic mass failed to relieve developing intractable intestinal obstruction. The patient died 23½ months after commencing initial postoperative chemotherapy.

Autopsy showed obstruction of the rectosigmoid by a grapefruit-sized tumor mass. There were only a few submiliary deposits of tumor in the abdominal cavity and no evidence of hepatic or extra-abdominal metastases.

DISCUSSION

x The marked regression of massive disseminated serous cystadenocarcinoma after combination chemotherapy was the most striking observation in this study. x There was only one case which failed to show some degree of objective response among the twenty patients with this pathologic lesion who were treated for two weeks or longer. This sensitivity of papillary serous tumors was in contrast to the resistance of the other histologic types treated. The objective response to chemotherapy would seem to be dependent on the proportion of papillary neoplasms compared to the more resistant types, especially the mucus cell adenocarcinomas in any given series. Since the potentially chemotherapy-responsive neoplasms comprise usually about seventy per cent (4) of random cases, it is not surprising that the minimum potential response of ovarian neoplasms (16) has been estimated by Karnofsky at about fifty per cent of all cases (Table II).

Our seventy per cent incidence of responses to antifol-alkylating agent therapy did not appear to be definitively better than the most favorable response rates employing single alkylating agents alone, viz. Green's 70 per cent symptomatic responses to hemisulfur mustard, and Masterson's 66 per cent responses to Chlorambucil. However, a detailed analysis of these and other recent chemotherapy reports suggests that, although the incidence of responses was not demonstrably better after combination therapy, the degree and the persistence

of objective tumor regression in comparable advanced cases appeared to exceed that previously obtained with single agents.

This is illustrated by the results of treatment with hemisulfur mustard alone compared with the alkylating agent-antifol combination among an equal number of advanced cases. Although Green was able to obtain 21 favorable responses in 30 cases of hemisulfur mustard therapy with some improvement in ascites, he observed only 8 cases with shrinkage of tumor masses. We found similar favorable responses, i.e.: 21 among 30 cases, but all of our patients showed marked objective regression of tumor masses. Differences in survival in this series may be significant since only 9 of Green's patients survived six months compared to 18 receiving combination therapy. Although such differences in survival and regression may be impressively in favor of the combination of agents, alternative explanations must be considered. Thus, differences in the case material or in

TABLE II
Survey of Response Rates

Drug	Author	Objective Responses
Radiogold.....	Combined	47%
TEM.....	Sykes	8/26
Hemisulfur Mustard.....	Green	21/30
" " " ".....	Rutenberg	9/14
Various Alkylating Agents.....	Coonrad & Rundles	17/38
Chlorambucil.....	Masterson	20/30
Thiotepa & Methotrexate.....	Greenspan & Fie- ber	21/30
Cytosan.....	Coggins	6/24
5-Fluorouracil.....	Young	3/7

the intensity or duration of chemotherapy could also account for such apparently more favorable results. Although the extent of disseminated intra-abdominal neoplasm appeared to be equal in both series, it must be noted that most of Green's patients represented the chronologically advanced Stage III disease recurrent after radiotherapy. Most of our cases were in a relatively fresh and presumably chemotherapy sensitive phase of diffuse intra-abdominal Stage IV dissemination.

The favorable comparison of chemotherapy with radiogold for Stage IV disease is suggested by the fact that only 47 per cent of cases selected for intra-peritoneal instillation of radiogold show some response (25), usually so transient that very few patients survive longer than six months. Although survival at the six month mark may be better with combination chemotherapy, the lack of important differences in the long-term survival of comparable cases must be emphasized (Table III). So far, less than thirty per cent of our patients survive one year after Stage IV disease. At 18 months and 24 months, there would appear to be little or no apparent differences thus far demonstrable between individual

chemotherapy, combination chemotherapy, or the various combinations of surgery, x-ray, or radiogold (1, 3, 4, 6, 25). The chemotherapy resistant state develops clinically in most cases between the 6th and 12th month after initiating treatment. Once this stage of recurrent growth with resistance to maximal doses of the combination has been reached, we have seen only an occasional subsequent worthwhile clinical remission from other agents. Despite the induction of tumor shrinkage after Cytosan in some combination resistant cases, there was only one among eight cases who was capable of resuming a normal ambulatory existence. The central problem remains one of finding agents which can effectively overcome tumor resistance without overwhelming the already debilitated host. At the same time the clinician must recognize tumor resistance early enough to allow such agents to delay or prevent the usual irreversible intestinal obstruction.

TABLE III
Survival of Advanced Cases

Author	Stage	No. Cases	Therapy	Survival			
				6 mos.	1 yr.	2 yr.	3 yr.
Green.....	III (IV)	30	H S M	8/30	1/30	?	?
Greenspan & Fieber.....	IV (III)	30	Thiotepa & MTX	18/30	7/30	0	—
Weed*.....	II & IV	41	x-ray, AU ¹³⁸ , HN ₂	?	0/41	0	—
Keitel.....	III & IV	44	“ “ “	?	?	3/44	—
Henderson...	II, III, IV	195	X-ray	?	?	?	28/195

* Stage II cases in this series had incomplete removal, by gross inspection, of tumor adjacent ovaries and parametrium.

SUMMARY

Thirty-two of a total of 35 patients with ovarian carcinoma completed a course of combination chemotherapy consisting of priming and maintenance doses of Thiotepa, with at least two courses of Methotrexate, four weeks apart. Abdominal biopsy only had been performed in 21 of 23 Stage IV cases so treated. Radiotherapy or radiogold had not been administered previously to any Stage IV patient. Twenty-one cases of objective tumor regression and clinical remission were obtained among the 30 Stage III and IV patients adequately treated. Regression of gross metastases and ascites was complete in 13 cases, with an excellent clinical remission averaging 6.9 months. Excellent and good results were obtained only among the various pathological forms of papillary serous cystadenocarcinoma. Serious toxicity in poor-risk patients occurred in cases associated with a malabsorption syndrome, an ileitis, and in one patient after a relatively recent course of total abdominal radiation. Survival following combination chemotherapy exceeded one year in 8 of 10 Stage II and III cases, but in only 7 of 23 Stage IV cases. The importance of accurate clinical and chronological staging at onset of chemotherapy was evident in assessing the extent of tumor regression and the effect on survival. The rapid oncolytic effect

in the Stage IV patient with serous cystadenocarcinoma, the relative safety of the combination of an antifol with an alkylating agent, and the development of tumor resistance are discussed.

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HEMODYNAMIC RESPONSES INDUCED BY INTRACAROTID INJECTION OF HYPERTONIC AND HYPOTONIC SOLUTIONS IN DOGS

MYRON R. SCHOENFELD, M.D., RICHARD P. LASSER, M.D., DOUGLAS F. ALLEN, M.D., AND CHARLES K. FRIEDBERG, M.D.

New York, N. Y.

INTRODUCTION

Holland *et al.* have described in rabbits the triad of apnea, bradycardia, and brief hypotension succeeded by more prolonged hypertension following the intracarotid injection of various hypertonic solutions, and indicated that this reflected "osmoreceptor activation" (1, 2). Eliakin *et al.*, working with dogs, alluded to the occurrence of apnea, bradycardia, and hypotension as characteristic of the response to intracarotid injection of hypertonic saline solution (3). Previous studies from this laboratory have shown that an "osmoregulatory reflex" may be provoked by injection of hypertonic solutions into peripheral arteries of dogs (4). The current research was undertaken to study the hemodynamic reactions in dogs which follow rapid intracarotid injection of solutions of varying osmolarity.

MATERIALS AND METHODS

Forty adult mongrel dogs 10-25 kg were studied, and a total of 430 intracarotid injections of hypertonic, isotonic, and hypotonic solutions were given.

Deep anaesthesia was induced by the initial intravenous injection of 35 mg/kg of pentobarbital. Cutaneous pain sensation was apparently abolished, as were corneal, canthal, and jaw reflexes, and no blood pressure or respiratory responses were elicited by crushing injuries of the toes or testicular compression.

Arterial blood pressures were recorded through a Cournand needle directed upstream in a femoral artery. Tracings were recorded via Statham and Sanborn transducers on a direct-writing, four channel recorder. The animals were given 50 mg of aqueous heparin to permit continuous recording of pressures over an extended period of time. Cardiac and respiratory rates were calculated from these tracings. Central venous pressures were recorded in ten animals through #8 Cournand cardiac catheters threaded up into the inferior vena cava from a femoral vein.

Injections were made directly into surgically exposed common carotid and external carotid arteries through an indwelling Cournand needle directed cephalad. The homolateral carotid sinus nerve was sectioned, the carotid sinus and adjacent portions of the internal and common carotid arteries were stripped of

From the Division of Cardiology, Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

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their adventitia, and the carotid body was removed. In three dogs, carotid sinus denervation was carried out bilaterally. The adequacy of the carotid sinus denervation was verified by failure of manual manipulation of the carotid sinus to evoke changes in the blood pressure or heart rate. The superior thyroid artery was ligated and sectioned. As the internal carotid and occipital arteries were of too small a caliber to allow direct needle puncture, injections were made into either one of these vessels by clamping the other two branches of the carotid trifurcation and injecting into the common carotid artery. In four dogs, injections were made into the common carotid arteries through Cournand cardiac catheters #5-8 threaded up via the aorta from a femoral artery under fluoroscopic control.

The following solutions were injected: saline (0.25% to 5%); dextrose (1.25% to 50%); urea (52.5 and 105 Gm per liter); and distilled water. Solutions of 5 per cent saline adjusted to a pH of 7.4 and to temperatures of 55, 70 and 100°F were also used. The volumes injected were 1-80 cc. Injections were made under manual pressure with syringes up to 100 cc in size. Injections of 30 cc, the most frequently used volume, took approximately 1 to 2 seconds. The onset and duration of the injections were recorded.

In twenty dogs, 194 intracarotid injections of 0.9-5 per cent saline or 5-50 per cent dextrose were made after bilateral vagotomy, after sympathetic ganglionic blockade, or after both of these procedures. Bilateral vagotomy was performed high in the neck just below the level of the carotid trifurcation. Sympathetic ganglionic blockade was induced by the intravenous injection of tetraethyl ammonium chloride (Etamon) in doses of 15 mg per kg body weight.

The circulatory reactions to intracarotid injection of 50% dextrose were observed in five dogs after complete transection of the brain at the medullopontine junction and after spinal cord transection at levels of C1-2. The level and adequacy of sectioning were verified postmortem by gross inspection and microscopic examination of sections of the brain and spinal cord taken at the level of the cutting.

Two dogs were injected with hypertonic solutions while in shock from an overdose of pentobarbital.

Responses to intracarotid injections were studied after intracarotid injections of protoveratrine A and B (Veralba) 0.1 mg in four dogs previously prepared with carotid sinus denervation and carotid body extirpation.

RESULTS

Injections of 1.4 to 10x hyperosmotic saline, dextrose, or urea solution into either common carotid artery produced several patterns of alteration in the arterial pressure, and cardiac and respiratory rates. It was found that identical responses were obtained when any two vessels of the carotid trifurcation were clamped and the injection made into the common carotid artery. If all three vessels were clamped, no response occurred. Bilateral carotid sinus denervation did not alter the reaction.

Following injection of 30 cc of 5 per cent saline, which was adopted as the standard procedure, the predominant reaction (48% of 194 trials) consisted of

systolic and diastolic hypotension, bradycardia or brief asystole, and a shrill prolonged expiratory cry followed by apnea (Fig. 1A). The range of the decrease in the systolic blood pressure was from 20 to 42 mm Hg, the mean fall being 20 mm Hg. The diastolic pressure fell to 30 to 48 mm Hg with a mean fall of 35 mm Hg. The heart rate decreased 50 to 110 beats per minute, with a mean fall of 80. The bradycardia began within 2 to 3 seconds after injection and lasted an additional 4 to 12 seconds. In some cases, complete asystole lasting as long as nine seconds was observed, with the blood pressure falling to zero. Some hypotension usually persisted even after return of the heart rate to control levels.

Respiratory slowing averaged 66 per cent of control rate with periods of apnea as long as 24 seconds. The response began 2 to 4 seconds after onset of injection and lasted $1\frac{1}{2}$ to 5 minutes.

In 23 per cent (45 trials) the intracarotid injection of 5 per cent saline elicited mild systolic and diastolic hypertension with bradycardia (Fig. 1B).

In 18 per cent (35 trials) mild arterial hypertension occurred without a change in heart rate or with slight tachycardia (Fig. 1C).

In 11 per cent (21 trials) mild hypotension occurred without a change in heart rate or with mild tachycardia (Fig. 1D).

Respiratory slowing tended to be most pronounced in animals exhibiting bradycardia and hypotension.

Identical, but quantitatively smaller, responses were provoked in the same animal by injections of dextrose solution and urea solution in comparable tonicity to 5% saline.

Qualitatively similar responses, though of much smaller magnitude were observed with 10 cc of 2.5 per cent and 1.25 per cent saline.

The temperature and pH of the injected solutions were excluded as causative of the hemodynamic responses by observing that 5 per cent saline adjusted to a pH of 7.4, and at temperatures below, at, and above body temperature elicited results identical with those obtained from stock solutions of pH 5.8 and 23°C. Nor did the circulatory changes seem to be secondary to the respiratory adjustments, for they occurred unchanged even when breathing was controlled by a mechanical respirator.

The response of inferior vena cava pressures was studied in 35 trials of intracarotid injection of 20 to 40 cc of 5 per cent saline or 50 per cent dextrose. The responses varied from a fall of 6 to an increase of 25 mm H₂O, the average change being an increase of 5 mm H₂O. The direction and magnitude of these changes were poorly correlated with concomitant changes in the arterial pressure, heart rate, or respiration. The venous pressure changes began with, or slightly preceded the onset of changes in arterial pressure, but usually did not reach a peak until 30 to 90 seconds after onset of injection.

Injection of 20 to 50 cc of hypotonic saline or dextrose solutions or of distilled water into the common carotid artery or its branches elicited either no hemodynamic response or quantitatively small responses usually consisting of slight hypertension, tachycardia, and tachypnea.

Thus, in the thirty trials in which 20 to 40 cc of distilled water was given

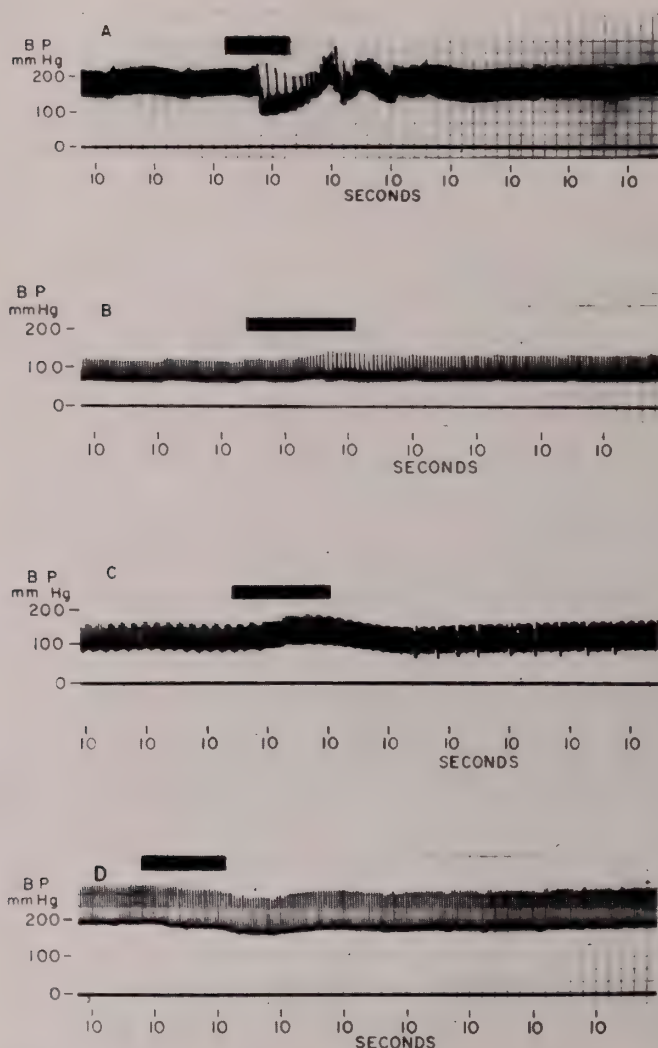
BLOOD PRESSURE RESPONSE TO INTRACAROTID
INJECTION OF 30cc 5% SALINE

FIG. 1. Patterns of circulatory response to intracarotid injection of hypertonic solutions. (A) Hypotension with bradycardia 48 per cent. (B) Hypertension with bradycardia 23 per cent. (C) Hypertension with an unchanged heart rate 18 per cent. (D) Hypotension with an unchanged heart rate 11 per cent.

by intracarotid injection, 17 showed hypertension and tachycardia. In these, there occurred a rise in systolic pressure of 5 to 30 mm Hg, with a mean rise of 10 mm Hg. The diastolic pressure rose 3 to 15 mm Hg, with a mean increase of 7 mm Hg. The heart rate increased 0 to 20 beats per minute, with a mean

acceleration of 10. The respiratory rate increased 10 to 40 per cent of control values with a mean augmentation of 20 per cent.

The effects of bilateral vagotomy and sympathetic blockage with TEAC, alone and in combination, are shown schematically (Fig. 2).

Following bilateral vagotomy those animals who had previously responded

BLOOD PRESSURE RESPONSE TO INTRACAROTID INJECTION OF HYPERTONIC SOLUTIONS

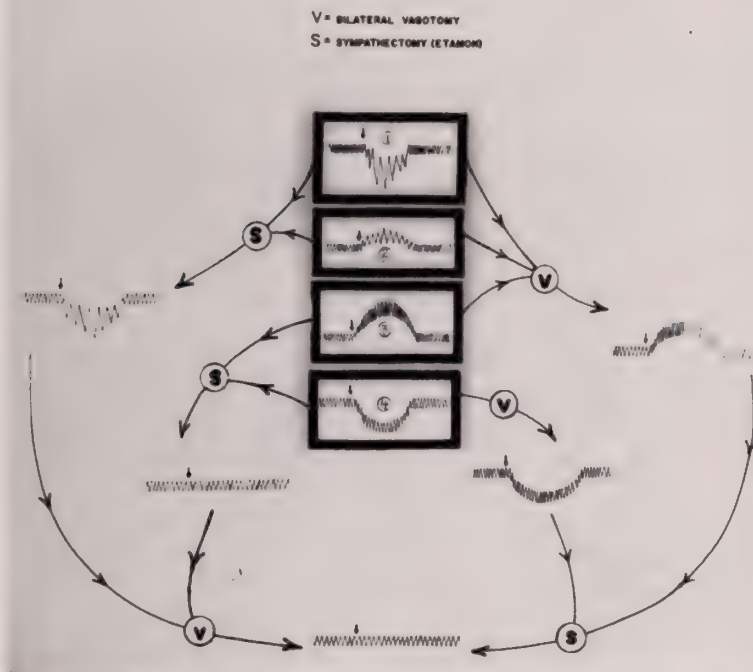


FIG. 2. Diagrammatic summary of the effects of bilateral vagotomy and sympathetic ganglionic blockade, alone and in combination, on the circulatory response to the intracarotid injection of hypertonic solutions. Blood pressure curves within the center rectangles symbolize the four major patterns of hemodynamic response of intact anesthetized dogs.

While complete description appears in text, note that bilateral vagotomy uncovers or intensifies sympathetic activity resulting from intracarotid injection in Types 1 to 3 sympathetic blockage uncovers parasympathetic effects. Thus both autonomic divisions are stimulated with each injection. The response of Type 4 is considered due to sympathetic vasodilatation.

to the intracarotid injection of hypertonic solutions by hypotension with bradycardia, or by hypertension with or without bradycardia, now uniformly manifested hypertension and tachycardia. The small number of animals who had manifested hypotension and tachycardia prior to vagotomy showed the same response following vagotomy. When these vagotomized dogs were next subjected to sympathetic blockade by intravenous administration of tetraethyl ammonium chloride, intracarotid injection of hypertonic solutions provoked no evident circulatory response at all.

In the reverse order, following sympathetic blockade in those dogs who had previously responded to intracarotid injection of hypertonic solutions by bradycardia with either hypertension or hypotension now uniformly manifested hypotension and bradycardia. Those which had previously responded with an unchanged or accelerated heart rate associated with hypertension now failed to respond at all. Bilateral vagotomy in these animals subjected to sympathetic blockade abolished all circulatory response. The responses were abolished, however, by spinal shock or by high cervical spinal cord transection after recovery from spinal shock.

Transection of the brain at the medullopontine junction did not alter the hemodynamic response to intracarotid injection of hypertonic saline or dextrose. The circulatory responses could still be provoked in dogs in deep barbiturate coma.

The influence of prior intracarotid injection of provera-trine upon the response to hypertonic solutions was next studied. While provera-trine itself (0.1 mg) provoked sustained hypotension, bradycardia and bradypnea, it did not block further blood pressure response to subsequent injection of hypertonic solutions.

DISCUSSION

As the injection of hyperosmotic saline, dextrose or urea into either common carotid artery or selectively into the internal carotid, external carotid or occipital arteries of dogs was found to induce pronounced circulatory effects, and as pH and temperature of the injected solutions, baroreflexes from the carotid sinuses and chemoreflexes from the carotid bodies were excluded as contributory factors, it was concluded that altered osmolarity of the injectate was the essential stimulus acting at some site within the distribution of these vessels, probably the central nervous system.

That circulatory responses persisted in animals subjected to brain transection at the medullopontine junction indicated the site of stimulation was situated below this level, probably in the medulla itself.

It also appeared as though stimulation both of parasympathetic and sympathetic outflow occurred with each injection of hypertonic solution, since one or the other effect could be uncovered by abolition of the other. Thus, for example, those animals who had initially responded with hypertension and bradycardia reacted, following bilateral vagotomy, with hypertension and tachycardia, while following sympathetic blockade they reacted with hypotension and bradycardia. This is not what would be anticipated if the autonomic centers were stimulated by a peripheral reflex mechanism (stimulation of the central end of cut vagus or peripheral nerve) where excitation of either autonomic division is attended by inhibition of the opposing division. Nor does it appear to be the reaction of a coordinated mechanism such as might originate from a definite osmocirculatory receptor center, for the responses would be anticipated to show a more basic consistency from animal to animal. These considerations have, rather, suggested that the circulatory and respiratory responses are due to direct stimulation of the autonomic medullary centers themselves.

That the site of stimulation was indeed in the brain, probably the medullary region, is supported by the observation that section of the brain at the medullo-pontine junction did not alter the response to hypertonic solutions, that the onset of hemodynamic response was noted to occur within 1 to 4 seconds following the onset of intracarotid injection, and that intravenous injection into the jugular vein did not elicit the same responses as intracarotid injection.

The finding that perfusion of any of the branches of the carotid trifurcation (when the other two were clamped) elicited identical circulatory responses does not preclude the possibility of localization of action within the medulla oblongata, for the anastomosis which exists between the internal carotid, external carotid, and occipital arteries can be considered as a functional unit (5).

The circulatory "chemoreceptor center" of Taylor and Page did not seem to be involved in the circulatory reactions elicited by the intracarotid injection of hypertonic and hypotonic solutions, for this "center" was paralyzed by veratrum while the centers on which the osmotic stimuli acted were not (6).

SUMMARY

Under pentobarbital anesthesia, the circulatory reactions of forty adult mongrel dogs to 430 intracarotid injection of 1-80 cc of hypertonic, isotonic, and hypotonic saline, dextrose and urea solutions and of distilled water were studied after denervation of the homolateral carotid sinus and removal of the carotid body.

Hyperosmotic solutions resulted in hypotension and bradycardia in 48 per cent of the trials. In 23 per cent of the trials, hypertension and bradycardia resulted. In 18 per cent of the trials, hypertension with an unchanged or accelerated heart rate resulted. In 11 per cent of the trials hypotension with an unchanged or accelerated heart rate resulted. Changes in inferior vena cava pressure were small and variable, averaging an increase of 5 mm water. Injection into the common carotid artery with any two of the three branches of the carotid trifurcation clamped, or direct injection into the common carotid or external carotid arteries yielded identical results.

Isotonic solutions did not evoke hemodynamic effects. Hypotonic solutions generally induced responses of small magnitude, but opposite to those achieved with hypertonic solutions in that particular animal.

The volume, temperature, and pH of the injected solutions, carotid sinus baroreflexes, carotid body chemoreflexes, and respiratory adjustments were excluded as the responsible factors in the circulatory reactions. The hemodynamic responses remained unaltered following brain transection at the medullary-pontine junction and during barbiturate coma, but were abolished by high cervical spinal chord transection or by spinal shock.

Intracarotid injections of hyperosmotic solutions following bilateral vagotomy resulted in hypertension and tachycardia in all animals except those few who had previously responded with hypotension and tachycardia or an unchanged heart rate; in these animals, bilateral vagotomy had no effect on the response achieved. Following sympathetic blockade with tetraethyl ammonium chloride,

animals who had previously reacted with bradycardia and hypertension or hypotension now uniformly responded with hypotension and bradycardia, while animals who had previously reacted with an unchanged or accelerated heart rate associated with either hypertension or hypotension now failed to react at all. A combination of bilateral vagotomy and sympathetic blockade abolished all response in every animal tested.

It is considered that these results can best be explained by postulating direct stimulation of the medullary autonomic centers. Definite evidence for the existence of an independent "osmocirculatory center" is lacking.

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THE ANTICOAGULANT PROPERTIES OF CHLOROQUINE DIHYDROCHLORIDE (ARALEN®), HYDROXYCHLOROQUINE SULFATE (PLAQUENIL®), AND QUININE DIHYDROCHLORINE

RESULTS OF TESTS IN VITRO

EDWARD H. MANDEL, M.D.

New York, N. Y.

INTRODUCTION

When chloroquine dihydrochloride is injected into the skin it produces local anesthesia and increased bleeding at the site of injection; subsequent tests, *in vitro*, have confirmed its activity as an anticoagulant (1). Since chemicals related to chloroquine, in either structure or function, might be more effective in preventing the clotting of blood, hydroxychloroquine sulfate and quinine dihydrochloride were selected for investigation. In the following study, the *in vitro* anticoagulant activities of chloroquine dihydrochloride, hydroxychloroquine sulfate, and quinine dihydrochloride are compared.

MATERIALS AND METHODS

Aqueous solutions of chloroquine dihydrochloride (50 mg cc)*, hydroxychloroquine sulfate (40 mg cc)*, and quinine dihydrochloride (50 mg cc)* were prepared for testing. Thirty vacutainer tubes were separated into six groups of five tubes each; these were filled with the chemicals alone and in combination as follows:

Group I 0.2 cc chloroquine dihydrochloride (10 mg)

Group II 0.225 cc hydroxychloroquine sulfate (10 mg)

Group III 0.2 cc quinine dihydrochloride (10 mg)

Group IV 0.1 cc chloroquine dihydrochloride (5 mg) and 0.125 cc hydroxychloroquine sulfate (5 mg)

Group V 0.1 cc chloroquine dihydrochloride (5 mg) and 0.1 cc of quinine dihydrochloride (5 mg)

Group VI 0.125 cc hydroxychloroquine sulfate (5 mg) and 0.1 cc quinine dihydrochloride (5 mg)

The controls consisted of six additional groups of five vacutainers each of which was filled with tap water in the amount corresponding to the total volume of solution of the chemical or chemicals being tested.

Five cc of venous blood was withdrawn by venipuncture from each of thirty healthy volunteers between the ages of thirty and fifty years. One cc of each aliquot of blood was placed into a tube containing the chemical or chemicals to be tested, and another one cc of this aliquot of blood was placed into the control tube. The times were recorded when the blood was obtained, when it

From the Department of Dermatology, The Mount Sinai Hospital, New York, N. Y.

* Supplied as a courtesy by Winthrop Laboratories.

had been placed into the tube with the test drug or drugs, and when clots had formed in each of the tubes.

RESULTS

The results are summarized in Table I. Each of the agents tested had anti-coagulant activity, but the duration of action of the hydroxychloroquine sulfate was approximately three times greater than the other drugs tested. When hydroxychloroquine sulfate was added to the other two chemicals, their anti-coagulant activity was not altered significantly.

TABLE I

Groups	Average Filling Time (min)	Range of Clotting Time (min)	Average Clotting Time (min)	Control, (Water) Average Clotting Time (min)
I. (10 mg of chloroquine dihydrochloride)...	1	17-28	22	5
II. (10 mg of hydroxychloroquine sulfate)...	1	59-78	69	5
III. (10 mg of quinine dihydrochloride).....	1	16-37	23	5
IV. (5 mg of chloroquine dihydrochloride and 5 mg of hydroxychloroquine sulfate)...	1	31-45	38	5
V. (5 mg of chloroquine dihydrochloride and 5 mg of quinine dihydrochloride).....	1	20-26	23	5
VI. (5 mg of hydroxychloroquine sulfate and 5 mg of quinine dihydrochloride).....	1	17-40	27	5

DISCUSSION

Madow used hydroxychloroquine sulfate (600-800 mg once a day) in the treatment of coronary artery disease, angina pectoris, thrombophlebitis, and intermittent claudication. He had selected the antimalarial drugs for study because of their "desludging" properties and preferred hydroxychloroquine sulfate because of its low toxicity (2). He stated that he believed that improvement of the circulation would result in the relief of pain produced by anoxemia and that this could be accomplished "without fear of inducing bleeding, such as can occur with the use of anticoagulants." Madow's results were good; he reported improvement in circulation, alleviation of pain in patients with angina pectoris, and prevention of the occurrence of thromboses and emboli. However, the disappearance of pain in the patients with angina occurred prior to the improvement of the circulation. Furthermore, the pain recurred promptly with the decrease or cessation of medication, and was subsequently relieved by increasing or reinstituting the hydroxychloroquine sulfate.

Vineyard successfully treated patients with pigmented purpuric eruptions

of the skin of the lower extremities with hydroxychloroquine sulfate (3). His interest had been stimulated by the work of Davis and Lawler (4) who demonstrated "intravascular sludging" in pigmented purpuric skin lesions, and by the report of Madow (2) of the "desludging" action of hydroxychloroquine sulfate.

Goodman and Gilman state that hydroxychloroquine and quinine act synergistically, *in vivo*, in the treatment of malaria (5). In the present *in vitro* study, however, hydroxychloroquine sulfate alone was more effective than its combination with quinine in preventing the clotting of blood.

SUMMARY

Chloroquine dihydrochloride, hydroxychloroquine sulfate, and quinine dihydrochloride, alone and in combination, were tested *in vitro* for their comparative anticoagulant activities. Each chemical had anticoagulant action in the test procedures employed, but the activity of hydroxychloroquine sulfate significantly exceeded those of the other two agents. Other studies of the "desludging" and anticoagulant properties of this group of chemicals are reviewed.

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ANGIOGRAPHY OF ISCHEMIC BRAIN DISEASE

LT. ALLEN SILVERSTEIN, M.C., U.S.N.R.

New York, N. Y.

Although the occasional complications of arteriography in patients with cerebrovascular disease are still stressed by some writers, the use of angiographic studies in patients with "strokes" continues to receive increasing general acceptance. Much information concerning the etiology, anatomic site of obstruction, and collateral circulation of ischemic brain disease has accumulated in the last fifteen years. The recent development of techniques to allow visualization of the more proximal cerebral circulation has resulted in new knowledge and still newer concepts. The purposes of this communication are to review much of this knowledge and to discuss some of these concepts. The inadequacies of clinical diagnosis, the arguments for and against angiography in patients with cerebrovascular disease, and the relative scarcity of complications from the procedure have been presented often enough in the literature, and will not be repeated here. In the further interests of brevity, no attempts at correlation or clarification of the arteriograms with clinical, experimental or pathologic material will be offered. The term "ischemic brain disease" as used here, is preferable to the less inclusive or descriptive phrases such as cerebrovascular disease, cerebral arterial insufficiency, stroke and cerebral apoplexy.

ARTERIOGRAPHIC FINDINGS IN PATIENTS WITH ISCHEMIC BRAIN DISEASE

The criteria both for selection of patients for angiography, and for arteriographic abnormality vary from clinic to clinic. In some cases, differences of opinion also exist as to the type of study (direct percutaneous puncture vs. catheter) to be performed and the arteries (aorta, innominate, carotids or vertebrals) to be visualized. The timing of angiography in relation to the onset of the clinical symptoms may also be controversial. The emphasis and material presented in the reporting of studies of cerebrovascular disease also vary with the major interests (diagnosis vs. anticoagulants vs. surgery) of the investigators.

Despite the differences of opinion, interests, and technique, there is some agreement on the arteriographic findings in large series of patients with ischemic brain disease. The accompanying table is an attempt to combine the observations reported in some of the larger series.

THE ANTERIOR CIRCULATION

It would appear that carotid artery disease is found in 13 to 28 per cent of "strokes," while middle cerebral artery occlusions are associated with 4 to

From the Department of Neurology, The Mount Sinai Hospital, N. Y., and the U. S. Naval Hospital, St. Albans, N. Y.

The opinions expressed are those of the author and do not necessarily reflect the policies of the Navy Department.

26 per cent, and anterior cerebral occlusions with 1 to 11 per cent. The most firmly established of the newer concepts of cerebrovascular disease is the frequency of extracranial carotid occlusions. The recognition of carotid stenosis has been greatly facilitated by routine visualization of the neck in all cerebral studies. The number of partial carotid occlusions demonstrated has increased tenfold by this maneuver (9).

Another new concept of carotid artery insufficiency is its reported relation to kinking, buckling, redundancy, elongation or extreme tortuosity of the

TABLE I
Angiographic Findings in Patients with "Strokes"

Author and Reference Number	Year Reported	Number of Patients Studied	Percentage of Patients with							
			Carotid Occlusion or Stenosis	Middle Cerebral Occlusion	Anterior Cerebral Occlusion	Basilar or Vertebral Occlusion or Stenosis	Hemorrhage or Edema	Arteriosclerosis	Normal Studies	Mass Lesions Including Aneurysms
Riishede (1)	1957	100	14	8	3	2	31	30	1	11
Rupprecht and Scherzer (2)	1959	1012	13	6	1	?	11	?	20	1.2
McDowell et al. (3)	1959	68	21	26	1.5	3	4	30	10	4
Frantzen et al. (4)	1959	93	12	15	5	?	4	32	31	10
Knighton and Gonzalez (5)	1959	144	28	A	A	?	?	A	45	Excluded
Baker (6)	1961	96	28	5	?	18	?	?	20	75
Bull et al. (7)	1960	80	18	10	2.5	2.5	8	?	58	1
Gurdjian et al. (8)	1960	585	25	4	11	3	2	?	19	11

A. 28% with "Diffuse Disease or Occlusion of Intracranial Vessels"

vessel (10-13). A recent angiographic study of one hundred consecutive patients with "strokes" revealed that 21 per cent had dilated or tortuous internal carotid arteries (10). In another study of 71 patients with cerebrovascular disease, 30 per cent had significant tortuosity or kinking of their carotid or vertebral arteries (12). Demonstration of the kinking was facilitated by angiography with the patient's head turned to either side. Significant stenosis at the site of the kink could thus be demonstrated. Attempts at alleviation of cerebral symptoms by resection of these kinks and coils have been reported (11). Carotid artery insufficiency, when the head is turned, may also result from compression by the lateral mass of the atlas (12).

Despite the increasing attention being paid to these changes in the internal

carotid artery, their responsibility for ischemic brain disease remains to be proved. We have seen several similar coiled, kinked or tortuous internal carotid arteries in elderly patients undergoing arteriography for subsequently proved tumors, subdural hematomas and other nonischemic conditions. We have not had much experience, however, in angiography with the patient's head rotated. The reported reduction in arterial lumina following this maneuver requires further study and confirmation.

Further problems arise in determining the significance of a minor degree of stenosis in the extracranial carotid, or in distinguishing arteriosclerotic narrowing of the intracranial arteries from congenital abnormalities or spasm (as in the case of subarachnoid hemorrhage, particularly when an aneurysm is not demonstrated). Errors in the diagnosis of carotid occlusion due to technical and other difficulties have recently been discussed elsewhere (14). The demonstration of collateral circulation, while of ancillary help in the recognition of large artery occlusion, should not be considered diagnostic by itself. We have seen visualization of the ophthalmic and then intracranial arteries following an inadvertent external carotid injection, and a perfectly patent internal carotid upon repositioning of the needle. The diagnosis of occlusion of the anterior cerebral artery should not be made from simple nonfilling. This artery can frequently be visualized by repeating the injection during compression of the contralateral carotid or by injection of that carotid.

THE POSTERIOR CIRCULATION

The true incidence of disease in the posterior circulation cannot be determined from the table, as vertebral studies were performed rarely, if at all, by the majority of workers included. In a report of 129 patients with cerebrovascular disease, 27 per cent were found to have vertebral-basilar involvement (15). Twenty-five per cent of the obstructive lesions demonstrated in patients undergoing surgery for extracranial occlusive disease in another study were in the vertebral and subclavian arteries (16). The frequency with which occlusions of the vertebral artery at its origin from the subclavian can cause basilar artery insufficiency is now being investigated. Vertebral artery disease may also produce well-defined intracranial syndromes, for example, that previously attributed to occlusion of the posterior inferior cerebellar artery.

Perhaps one of the most significant of the new concepts of interference with the posterior circulation is its reported production by compression of the vertebral arteries by cervical osteophytes. This has been demonstrated by catheter arteriography with either oblique views (17) or extension and rotation of the neck (18). Reports of complete relief of symptoms of basilar artery insufficiency following excision of a compressing arthritic spur or cervical fusion have already appeared (12, 19).

Just as in the carotid circulation, differentiation between an arteriosclerotic vertebral artery and an anomalous one may be difficult. Variations in the origin of the vertebral artery (e.g. from the aorta) may lead to a spurious diagnosis of occlusion during subclavian angiography (15). The diagnosis of posterior

cerebral occlusion should not be made before both vertebral and ipsilateral carotid arteriograms have been carried out.

ARTERIOSCLEROSIS

Arteriographic findings thought to be indicative of arteriosclerosis are reported in approximately thirty per cent of patients with "stroke" syndromes. Differences of opinion exist, however, as to what constitutes arteriosclerosis in an angiogram. Some workers, not included in the table, include stenosis of large vessels as part of arteriosclerosis. Other findings sometimes cited as evidence of arteriosclerosis are abnormalities of the angulation of the vessels at the bifurcation of the internal carotid in the AP projection (the so-called T junction) (20); inability of the smaller arteries to fill (1, 3); delay until the venous phase in the visualization of the small arteries (1); and delayed circulation in the internal carotid as compared with the external (1). Some of these changes can be produced by faulty injection. Moreover, even with good technique, there is considerable doubt as to their significance.

There is more agreement that tortuosity of the vessels, variations of their caliber, and irregularities of their walls are fairly reliable signs of arteriosclerosis. There are some difficulties, however, in the interpretation of these findings, and their exact relation to the clinical picture of ischemic brain disease remains uncertain. Bull, *et al.*, have recently reported an interesting, well-designed attempt at evaluation of the reliability of the arteriographic signs of arteriosclerosis (20). Twenty-three nonobstructed arteriograms of patients with acute "strokes" were matched for age, sex and side of injection with the same number of arteriograms of patients without cerebrovascular disease. All films were read twice without any history by three qualified radiologists. Considerable interobserver as well as intraobserver variation in the reporting of arteriosclerosis was demonstrated. The only findings which correlated with clinical cerebrovascular disease were variation of the caliber of vessels and irregularities of the walls.

OTHER FINDINGS

The demonstration of vascular displacement without other abnormality in the arteriograms of patients with "strokes" is usually thought to represent intracerebral hemorrhage. These findings, which could just as readily be explained by edema, have been reported in 2 to 31 per cent of patients in the table. Although subsequent study has usually shown some return towards normal, the possibility of an avascular mass remained in a few patients. Various mass lesions, including aneurysms, have been found in from 1 to 11 per cent of patients with typical histories of strokes. Perhaps the most common error in clinical neurology (although not necessarily made by neurologists), is the labeling of hemiparesis in a middle-aged or elderly patient as a "stroke." That many of these patients actually have cerebral neoplasms or subdural hematomas remains the best argument for the performance of arteriography (21).

There now remains a large group of patients, from 1 to 58 per cent in the table,

with "strokes" in whom angiography fails to demonstrate any abnormality. The explanation for these normal angiograms is twofold. First, no one intracranial vessel may be occluded, or the vessels involved may be too small to visualize at arteriography. This might be particularly true for arterioles supplying the internal capsule. A short time ago we started injecting the freshly removed brains of patients with ischemic brain disease and normal arteriograms (which are quite common in our experience) with a barium-gelatin mixture. This allowed better visualization of the smaller vessels when the brain was subsequently x-rayed than did angiography performed during life. We hope to learn something about possible small vessel occlusions by comparison of these films with the pathologic distribution of infarcts or ischemic changes, if any.

The second possible explanation for normal arteriograms in "stroke" patients is that the diseased artery may well be proximal to the site of injection. The current trend for angiographic investigation of ischemic brain disease is the development of techniques to allow visualization of the vessels closer to the heart.

TECHNIQUES FOR ANGIOGRAPHY OF ISCHEMIC BRAIN DISEASE

The principle of the current neuroradiologic trend can be summarized simply: the needle has been placed further and further away from the brain. The trend probably began with the routine study of the origin of the internal carotid during direct percutaneous carotid injections. Efforts were then directed toward visualization of the innominate and left common carotid arteries. We (together with Dr. R. Mones) had some success doing this three years ago by inserting the needle downwards into the carotid and compressing distal to it at the time of injection. This technique has recently been redescribed (22). These large vessels can also be studied by passing a catheter down the carotid, a technique which also allows study of the vertebral arteries (23). Direct vertebral puncture with the modified Sheldon needle with the hole facing proximally may also allow full vertebral visualization (24).

Percutaneous subclavian puncture for vertebral arteriography was introduced in 1957 (25), and applied to the study of vertebral-basilar artery disease the following year (26). To avoid the frequent complication of pneumothorax, a more medial approach for subclavian puncture has been suggested recently (27). Catheterization of the subclavian artery for carotid as well as vertebral investigation has also been reported (28). Techniques for visualization of the vertebral and right carotid circulation by direct injection of the right brachial artery have also been described (29, 30).

Although cutdown catheterization techniques for vertebral arteriography have been in existence for some time, percutaneous femoral catheterization for this purpose was introduced in 1956 (31). The Seldinger catheter (which allows a larger quantity of contrast substance to be injected) was employed within two years (32, 33). The technique which seems to offer the greatest promise at present is that of percutaneous brachial artery Seldinger catheterization (18, 34), which not only allows investigation of the vertebral and subclavian arteries,

but also of the entire carotid, innominate and aortic arch (17). The term panangiography has been applied to this technique. Attempts at total cerebral arteriography by either rapid intravenous (35, 36) or intra-aortic (13, 33) injection of large quantities of contrast matter have generally not produced adequate intracranial visualization. While many of the techniques cited above are satisfactory for proximal artery study, they have not provided intracranial contrast as well as the older direct carotid or vertebral punctures. This is especially true for brachial arteriography and, at times, for catheter studies when the tip of the catheter has not been advanced far enough.

Much remains to be learned about functional intracranial circulatory changes and collateral circulation in patients with ischemic brain disease. Perhaps further application of the angiographic techniques of rapid serial (37), biplane stereoscopic (38) and cineradiographic (39) study to cerebrovascular disease will be rewarding.

SUMMARY

Some of the reported angiographic studies of patients with "strokes" have been described, and the nature and incidence of the findings tabulated. Disease of the extracranial circulation has been found often, and its possible production by certain mechanical factors has been discussed. The angiographic diagnosis of arteriosclerosis, the frequently normal angiogram, and the techniques for investigation of ischemic brain disease have been reviewed briefly.

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Clinico-Pathological Conference

ALCOHOLISM WITH PROTRACTED "OBSTRUCTIVE" TYPE JAUNDICE

Edited by

FENTON SCHAFFNER, M.D.

New York, N. Y.

A 48 year old male unemployed clerk of Irish descent was admitted to The Mount Sinai Hospital because of jaundice of six months duration. This was associated with a twenty pound weight loss and with nausea and vomiting for the previous two weeks. He never noticed hematemesis, melena, pruritus, abdominal pain or food intolerance. He had consumed a pint or more of whiskey daily for over thirty years. Seven months prior to admission he was hospitalized for one week because of alcoholic hallucinations at which time he was noted to be jaundiced. He took chlorpromazine and other tranquilizers intermittently and has also received many shots of B vitamins. His urine had been dark for several months but his stools were never light. At the age of 7 he had an appendectomy and at the age of 8 he became jaundiced for the first time for several weeks. He was again jaundiced at age 16 and at age 30 for several weeks. He had pneumonia at age 19. The remainder of the past history and the family history were noncontributory.

On examination he was afebrile with normal blood pressure and respirations. His pulse was 110 and irregular with periods of bigeminy. He was deeply jaundiced and lethargic but restless. Telangectasia were noted on the face and chest but no spider nevi were seen. The eyes, ears, nose, throat and neck were normal, except for icterus. No fetor hepaticus was detected. The lungs were clear. The heart was slightly enlarged to the left and there were many premature contractions but no murmurs were heard. The liver edge was 8 fingerbreadths below the costal margin and it was firm, irregular and not tender. The spleen tip was felt. No ascites was present. A fine tremor was found but it was not flapping. The reflexes were normal. The remainder of the examination was normal.

Laboratory findings are summarized in Table I. No significant urinary abnormalities were recorded. In addition, many differential counts showed a leukocytosis with no abnormal cells. Platelet counts were normal. The erythrocyte sedimentation varied between 32 and 44 mm hr. Venous pressure and circulation time were normal. Tuberculin skin tests were negative. Hemoglobin was all type A. Low serum albumin and slightly elevated alpha globulin fractions were found on electrophoresis. Electrocardiograms revealed nonspecific ST and T wave changes. X-rays of the gastrointestinal tract showed no intrinsic abnormalities. Intravenous pyelogram was normal and a left pleural effusion was seen in a chest x-ray.

From the Department of Pathology, The Mount Sinai Hospital, New York, N. Y.

During the first month in the hospital, his jaundice remained unchanged but his mental condition cleared. He had ascites, afternoon temperature spikes to 100° or higher, dark guaiac-positive stools, anemia, leukocytosis to over 40,000/mm episodes of paroxysmal atrial tachycardia and several spider nevi on his anterior chest. He was treated with vitamins, liver extract, aluminum hydroxide gel and several blood transfusions.

During the second month in the hospital, he had a left pleural effusion, more episodes of paroxysmal tachycardia, lethargy, flapping tremor and diarrhea with 12 to 15 bowel movements a day. Fluid obtained by diagnostic paracentesis was

TABLE I

	1st Admission				2nd Admission
	On Admission	1st month	2nd month	3rd month	On Admission
Hg (Gm%)	13.3	9.6	8.8	12.7	10.5
WBC (mm ³)	14,900	32,000	45,000	11,800	14,200
Prothrombin time (sec.)	14	23	18	18	17
BUN (mg%)	16	17	9	8	9
Glucose (mg%)	116	101	—	80	71
CO ₂ (mEq/l)	—	25.4	20.3	19.4	24.3
Cl (mEq/l)	—	88	102	104	102
Na (mEq/l)	—	133	134	139	139
K (mEq/l)	—	3.5	3.6	3.2	2.5
Albumin (Gm%)	3.7	2.5	2.2	2.5	2.8
Globulin (Gm%)	3.7	3.5	3.7	3.2	3.3
Bilirubin (mg%)	16.2	14.4	—	15.0	3.3
Ceph. flocc.	0	1+	2+	1+	3+
Thymol turb. (units)	2.0	1.2	—	—	—
SGOT (units)	107	150	80	6.4	sl. elev.
Alk. phosphatase (K-A units)	15.3	25.2	31.3	—	16.6
Cholesterol esters (mg%)	326/207	250/168	—	190	185
Ammonia (mc/ml)	4.5	2.4	2.7	—	—
Stool guaiac	2+	4+	0	0	4+

yellow and clotted. The cell count was 185/mm³ with 60% mononuclear cells, 30% red blood cells and 10% mesothelial cells. No cancer cells were seen on smear or in a block. The fluid was sterile.

After 72 days in the hospital, the patient rather dramatically began to recover. His appetite improved, his jaundice and diarrhea (apparently related to quinidine therapy) lessened, and on the 80th day he was sent home on a regimen of quinidine, vitamins, belladonna and a low salt diet.

About ten days after discharge his physician felt that ascites was increasing, and he was given hydrochlorthiazide. Three days later he was awakened from sleep by vomiting of coffee-ground material. He was confused and was hospitalized at another hospital. After two days he became clear mentally and was transferred here.

He had a temperature of 99.4°, a regular pulse of 108/min. with normal blood

pressure and respirations. He was poorly nourished and jaundiced. Many spider nervi were found on his chest, shoulders and back. The neck veins were full at 30°. Severe gingivitis was present. The breath sounds were diminished in both lung bases. Massive ascites distended the abdomen and the liver could not be felt. The feet were edematous and slight pretibial edema was noted. No flapping tremor was seen.

Laboratory data are in Table I.

In the hospital he had some diarrhea and vomited repeatedly. He was given belladonna, aluminum hydroxide, potassium triplex, quinidine, neomycin, vitamins, liver extract and vitamin K. He was found dead in bed after 48 hours in the hospital.

*Dr. Alexander B. Gutman**: The problem, as I see it, is that the patient ran a course consistent with advanced cirrhosis of the liver of a type that we will discuss, with terminal hepatic insufficiency, but the laboratory data indicate a form of obstructive jaundice. The main problem that I have had in wrestling with this case is to find some way of reconciling the clinical impression with the laboratory findings.

We cannot neglect the story of three episodes of jaundice earlier in life. Did he have one of the constitutional diseases associated with a hemolytic type of jaundice which may begin at this early age? His subsequent history denies this so we can discard the possibility now. Did he have a different kind of familial or inborn type of jaundice such as Dubin-Johnson's syndrome, which may begin at this early age and be manifested by recurrent jaundice? I think that the subsequent history is inconsistent with this possibility and I shall discard that. Did he as a result of his appendectomy have some inflammation of the portal vein and its tributaries i.e. pylephlebitis? He has such a long period free of all symptoms and signs; it seems unlikely that there would be an interval of forty years between the onset of his phlebitis and the development of his severe jaundice. I can conclude only that as a youngster he probably had recurrent attacks of infectious hepatitis, and this will have an important bearing on the subsequent analysis of the case.

Therefore, we have an Irishman age 48, who while still a youth was subject to recurrent attacks of jaundice, and who became a heavy drinker. He later developed severe jaundice persisting for possibly a year or so, associated with weight loss, nausea and vomiting, without any other indications of interest or significance from the etiological point of view. He had a large, firm, irregular liver eight fingerbreadths below the costal margin.

X-rays of the gastrointestinal tract were obtained. Do you have those here?

Dr. Mansho T. Khilani†: On the first admission the gastrointestinal tract as far as we could see was normal. The chest examination at this time showed elevation of the diaphragm and some atelectasis at both bases. There was a small effusion on the left side.

* Physician to the Hospital, The Mount Sinai Hospital, N. Y.

† Research Associate in Radiology, The Mount Sinai Hospital, N. Y.

Dr. Gutman: Did you examine the esophagus for varices at this time?

Dr. Khilani: The esophagus was normal at this time, as was the stomach.

Dr. Gutman: We would not be very surprised if the effusion was on the right, but on the left perhaps it takes on a little more significance in a patient who is not in congestive failure.

We can get an idea of what the thinking was on the service when we look over the method of treatment. The patient was given vitamins, like every alcoholic with cirrhosis, liver extract—I do not know that it has ever been established to do any good but I see it is still given—and aluminum hydroxide gel with the thought that he might have a peptic ulcer; 10 to 20 per cent of cirrhotics do have peptic ulcers. He also received several blood transfusions. The jaundice persisted. In the second month in the hospital, the effusion in the left chest became more pronounced. There was nothing else in this lung, was there?

Dr. Khilani: No.

Dr. Gutman: With all the ascitic fluid in the abdomen, perhaps the effusion was not as significant as it might have been otherwise.

The development of diarrhea in the course of cirrhosis always worries me because it may be a terminal event, and in the pre-antibiotic days we used to see phlegmon, usually of the large bowel but sometimes of the small bowel, which manifested itself in this way. Demise would follow within a week or two. The subsequent course rather suggests that this was not the case because he did improve temporarily.

Clinically, I think this is a picture of advanced cirrhosis of the liver, leaving open for the moment the question of what kind of cirrhosis we are dealing with. The first real shock comes when we examine the laboratory data. The serum bilirubin was high but towards the end, for some reason, it declined. We expect on the basis of what we have heard that he would have a strongly positive cephalin flocculation test but it was negative for some time and only weakly positive later, finally 3+. We would expect that his transaminase would be very high; it was elevated but not really in the range expected for a patient who had active hepatitis, and later fell to normal. Thymol turbidity was equally disappointing. The serum alkaline phosphatase, on the other hand, rose during the period of leukocytosis to fairly high levels, but fell off terminally. The serum cholesterol esters, instead of being low, were quite normal; in fact, even a little elevated at the beginning. The serum globulins were somewhat elevated but not consistent with the usual changes in postnecrotic cirrhosis.

How are we going to fit these two discordant aspects of the story together? I think all of us trained in the classical school would say promptly that he had Laennec's cirrhosis, a term that pathologists now disdain, but by which we mean alcoholic cirrhosis. There is no way of being sure, that I know, if a patient does or does not have a hepatoma, so this must remain under consideration. The reason I equivocate about Laennec's cirrhosis is that in the last decade or so, the incidence of viral hepatitis, even in patients who have an alcoholic history and who have portal fibrosis which we ascribe to alcohol or malnutrition, is becoming more common. Dr. MacDonald in Boston reported from the Mallory Insti-

tute (and I believe that Dr. Popper's and many others' experience coincides with this) that he was seeing much more postnecrotic cirrhosis today than Laennec's cirrhosis, even in alcoholics.

In view of the severe hepatic insufficiency in this patient and his history of early jaundice, I propose that whatever mark alcohol made on his liver, there is now a good deal of hepatocellular necrosis, some of which is of viral origin.

All of this, still does not explain the primarily obstructive laboratory picture. Did he have some lesion causing extrahepatic biliary tract obstruction, such as a carcinoma of the pancreas, chronic pancreatitis, a stone in the common duct or a tumor of the ampulla? I do not see anything in the history that gives us the privilege to ascribe the obstruction to some lesion of the extrahepatic biliary tract, and therefore it seems to me we have to consider the possibility of intrahepatic biliary tract obstruction. This could be from viral hepatitis, which is primarily or principally cholestatic in its effects. It causes what I like to call intrahepatic biliary tract obstruction (not a very good phrase, as Dr. Popper has properly pointed out) which leads to the clinical picture of more obstruction, higher alkaline phosphatase activity and less evidence of hepatocellular damage than one would ordinarily expect. This is a possibility that I will not rule out.

Is this the picture of chronic biliary cirrhosis? It seems to me that the degree of hepatocellular damage is such as to discourage this notion, and I am not going to call this biliary cirrhosis. I think this is a combination of portal or septal cirrhosis, with superimposed postnecrotic cirrhosis, and I am at a loss to account for the degree of obstruction that we see here, unless it is due to the so-called cholestatic form of viral hepatitis.

I would like also to raise another possibility, and that is that he might have acquired tuberculosis. I raise this possibility although I appreciate the fact that, whereas tuberculosis was a common complication of Laennec's cirrhosis in the old days, it is much less common today. About two or three per cent of patients with Laennec's cirrhosis have terminal tuberculosis but there are several things that alert me to the possibility here. One is the leukocytosis that developed. The second is the unexplained pleural effusion on the left, and then on the right. I admit this is not very good evidence, nor is the nature and quantity of the peritoneal fluid, under these circumstances. I cannot be very concrete about his rapid demise. I have no ready explanation for the cardiac irregularity except the possibility that he, like so many others of Irish descent, may have acquired a rheumatic heart lesion.

*Dr. Milton Mendlowitz**: It was a very puzzling case because all along one of the possibilities was of a complicating neoplasm. But there was nothing to support this. Finally he was discharged with a diagnosis of Laennec's cirrhosis.

Dr. Gutman: Neoplasm still remains a distinct possibility.

Dr. Alexander Richman†: I would like to ask if he ever had a liver biopsy. I

* Attending Physician, The Mount Sinai Hospital, New York.

† Associate Attending Physician for Gastroenterology, The Mount Sinai Hospital, New York.

am interested in the possibility that the episodes of jaundice in childhood were related to Dubin-Johnson disease because, while he might have had recurrent attacks of hepatitis, it is more likely that they were due to a Dubin-Johnson or Gilbert's disease. In view of the evidence of hepatic dysfunction, it would not have been very easy to demonstrate this by laboratory tests.

Dr. Mendlowitz: He was never well enough.

From the floor: I would agree with Dr. Gutman that the possibility of a hepatoma is to be considered here. Also, I am interested in the elevated serum alkaline phosphatase, as that to me would be evidence of some infiltration. I would think that this man probably had cirrhosis of the liver with a hepatoma and, as some explanation for the previous bouts of jaundice, consideration should be given to the possibility of a Dubin-Johnson or Gilbert's disease.

From the floor: If one makes the diagnosis of a hepatoma, how do you account for the sudden improvement?

Dr. Gutman: It is rather difficult but of course it was a short-lived improvement.

Dr. Hans Popper:* At the autopsy of this patient, there was dilatation of both venous and arterial vessels in the cutaneous layer of the skin below the epithelium. These very rapidly developing arterial-venous anastomoses may be a result of an endocrine disturbance since the same type of lesions appear and disappear in pregnancy.

In the brain we could find no evidence of hemorrhage. We know that subdural hemorrhages are frequently found in alcoholics. On section we saw brain edema with some swelling of the dura.

There was a significant amount of osteoporosis with reduction of the trabecular network. In the marrow no hemolytic hyperactivity or any other abnormality was recognizable in the usually somewhat mishandled autopsy specimen of paraffin embedded bone.

There was a small adenoma of the thyroid and a combination of involution and hyperplasia reflecting the prolonged stress to which this patient was exposed. In the lungs some effusion was present but there was no tuberculosis or even bronchitis. We could not find a fat embolism. Multiple small fat embolisms are usually thought to be a cause of acute death in the alcoholic.

The heart was somewhat enlarged. It weighed 350 grams. The fatty tissue here had a brown tint which we see quite often in the alcoholic. There were no rheumatic changes. Slight hypertrophy of the heart muscle fibers was seen on the histologic sections. As we looked at the fibers with very high power, we saw some black pigment. This is considered the result of malnutrition and some have linked it with tocopherol deficiency. Other changes, such as an increase of nuclei and slight breakdown of the muscle with accumulation of cells, such as were seen in this case, probably were reflections of electrolyte imbalance in this patient dying apparently in coma and hepatic failure.

Slight arteriosclerosis, with a rather bland aorta, was found, giving further background of this patient, again emphasizing his age.

* Pathologist-in-Chief, The Mount Sinai Hospital, New York.

The testes showed complete absence of spermatogenesis, with marked thickening of the basement membrane indicative of fairly advanced atrophy. In the prostate, adenomatous hyperplasia was seen.

One feature is considered to be an estrogenic effect, namely, squamous cell metaplasia with normal glandular epithelium.

The adrenal gland was in surprisingly good shape. Sometimes under these circumstances adrenal insufficiency may play a role. Histologically, this was surely not a depleted adrenal.

The kidneys showed a moderate degree of jaundice but were otherwise well preserved. There was no evidence of any histologic change. On microscopic examination, the glomeruli appeared entirely normal but brown pigment was deposited in the distal convoluted tubules and large bile stained casts accumulated in the medullary portion. Many consider that this biliary nephrosis may lead to renal insufficiency. However, these casts have very little effect upon the surrounding epithelium, which was quite well preserved, and I feel that biliary nephrosis interferes as little with renal function as jaundice with the function of the skin. In the proximal convoluted tubules, fine fat droplets were found at the base of the epithelial cells. This has been described in fatal hepatitis and in all conditions in which very marked hepatic decompensation is present.

Along the gastrointestinal tract, the esophagus was normal, with some very slightly dilated veins. There were some small ulcerations in the cardiac portion of the stomach and the veins here may have been a bit larger than normal. However, portal hypertension could certainly not have been recognized from this area. The colon showed distinct edema. This has been described in acute yellow atrophy, sometimes associated with phlegmonous changes. It has also been associated with hypoalbuminemia. Since only edema was present without any phlegmonous change, we have a hypoproteinemic type of edema of the colon.

In the pancreas a large cyst containing brown material was found, representing an old hemorrhage. This was the residual change of a chronic pancreatitis in which an acute episode was present.

The spleen was larger than normal, weighing 250 grams. It was fleshy in appearance but it was not the large spleen which would have been expected with long-standing alcoholic cirrhosis. Microscopically, we saw endothelial hyperplasia with some blocked sinuses and plasma cells, suggesting gamma globulin formation, probably as a result of some antigenic stimulus. There was a large amount of PAS-positive material deposited in the littoral cells which we assume to be carbohydrate-containing tissue breakdown products; this probably accounts for the enlargement of the spleen, more than portal hypertension. There were a few areas of increased fibrosis but most of the spleen was normal, suggesting incipient portal hypertension. There was so little iron in the spleen that hemolytic jaundice could be eliminated.

The liver weighed 1750 grams, only a bit larger than normal. We could not make out the architecture clearly and no hobnail appearance was present (Fig. 1). The common duct was normal, with no evidence of any obstruction. Low power views of histologic sections presented quite a confusing picture. The cells

were irregularly arranged, and marked infiltration was present throughout the parenchyma. This was not massive necrosis. Hepatitis seemed to be our best diagnosis and we looked further. We saw severe portal tract infiltration, bile duct



FIG. 1. Cut surface of liver showing loss of architectural pattern but no distinct nodules.

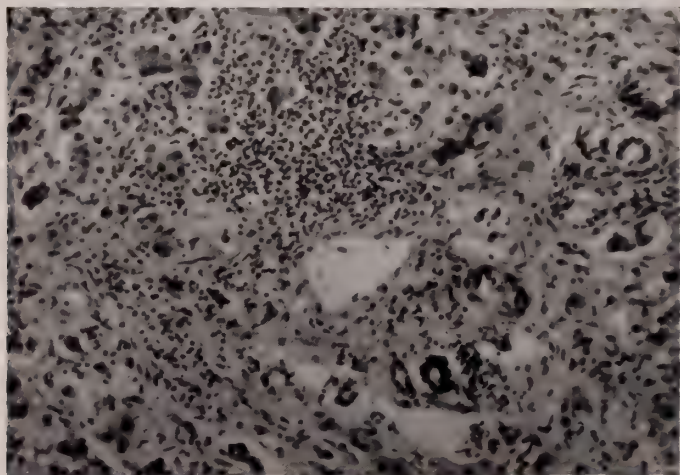


FIG. 2. Portal inflammatory reaction with ductular cell proliferation and irregular liver cells on the lobular periphery. (H & E $\times 63$)

proliferation and irregular arrangement of the liver cells (Fig. 2). This was a fairly acute hepatitis without indication of an etiology.

Dr. Gutman predicted that we would find evidence of intrahepatic cholestasis and we did. It was probably subsiding. The patient had only 3 mg% of serum bilirubin at the time of death and that was the reason more cholestasis was not seen, although there was probably much more earlier.

In some of the liver cell plates, transformation into acini was seen (Fig. 3), which occurs in the cholangiolitic type of hepatitis. There was too much liver

cell damage, however, and this could not be the basic lesion, either from the clinical picture or from what we have already seen histologically. In connective stained sections, irregular sears with beginning perilobular fibrosis and some beginning nodule formation were seen (Fig. 4). A tremendous number of

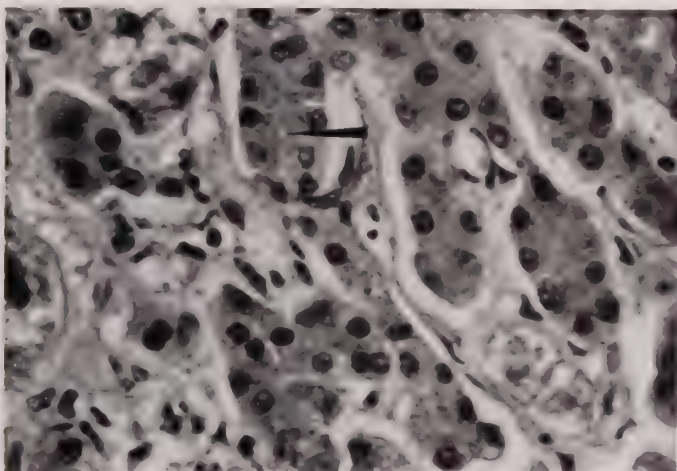


FIG. 3. Alveolar transformation of liver cell plates arranged around canaliculus (arrow) as a reflection of bile stasis. (H & E $\times 440$)

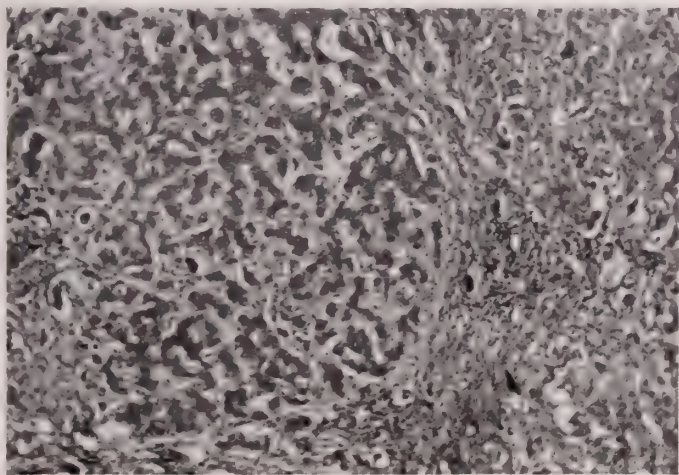


FIG. 4. Beginning nodule formation. (Mallory $\times 120$)

liver cells were breaking down but they were also regenerating. Many leukocytes were seen. There was distinct fibrosis around each liver cell, which is not seen in viral hepatitis (Fig. 5). Fatty metamorphosis may occur late in viral hepatitis. The amount of fat present is not as significant as the fact that the fat itself in this case caused an inflammatory reaction. Around the fatty cysts there was a distinct inflammatory reaction which we call lipogranuloma where the fatty material acts like a foreign body.

This occurs typically in alcoholics and is a type of acute alcoholic necrosis. To confirm the presence of acute alcoholic necrosis, we had to demonstrate characteristic breakdown products in liver cells. Mallory described a hyaline

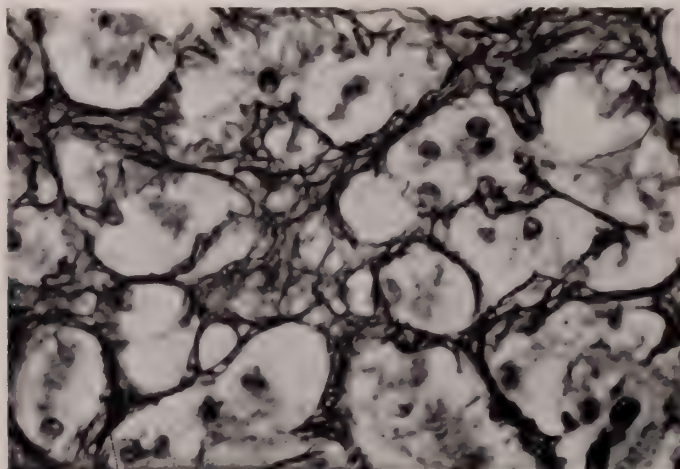


FIG. 5. Increased fibers around liver cells and small areas of collapse (silver impregnation). ($\times 440$)

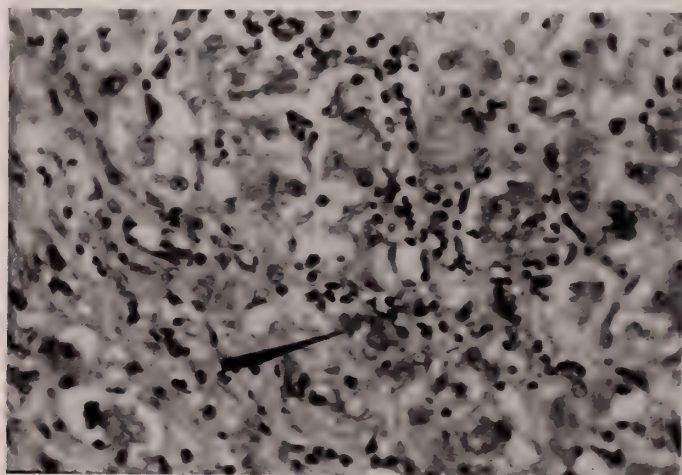


FIG. 6. Mallory's alcoholic hyaline (arrow) in large cells surrounded by leukocytes. (H & E $\times 250$)

body found in many liver cells (the term "hyaline," however, is not quite appropriate). The Mallory body is rarely found in any other liver condition and here it must be considered indicative of acute alcoholic necrosis. The Mallory body takes a bluish color with the stain which Mallory described. The bluish bodies appear ramified because they arrange themselves around the nucleus in an irregular fashion. They lead to necrosis of the liver cell but this is a peculiar type

of necrosis because, in contrast to viral necrosis, it attracts leukocytes around the disintegrating liver cells (Fig. 6), and leads to fibrosis. We could demonstrate in many specimens that the disintegrating cells were sites of fiber formation. Part of the fibrosis resulted from this necrosis and disappearance of the liver cells. This necrosis led to proliferation of ductules. The lumen of the ductules contains the material formed by cell breakdown. I feel that this acts as a stimulus for ductular proliferation. The ductules are surrounded by extensive fiber formation. Thus there are fibers around necrotic cells and also around ductular proliferation.

In addition, Mallory bodies and extracellular fat act as irritants and we saw formation of multinucleated giant cells in the liver (Fig. 7). Sometimes a few

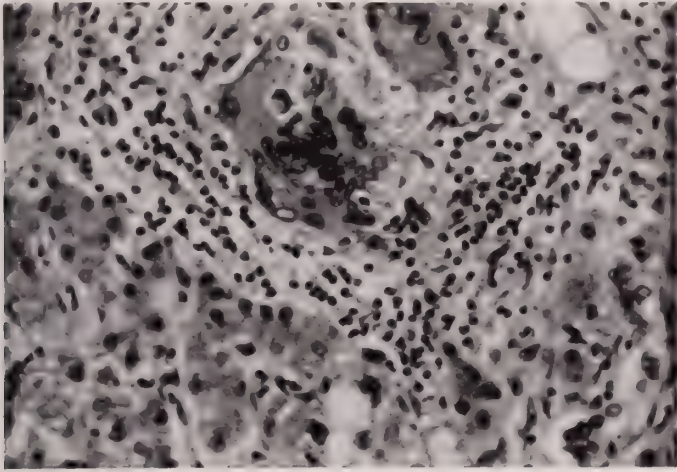


FIG. 7. Giant cell formation in granulomatous reaction around Mallory bodies and extracellular fat. (H & E $\times 250$)

sarcoid-like particles are found with acid-fast stain. Mallory bodies are distinctly acid-fast, probably because they contain some lipoid which is the irritating material. Similar to tuberculosis and sarcoidosis, this material produces changes in the vessels and, in this case, hepatic vein branches showed an endophlebitis which is seen quite often in alcoholics (Fig. 8).

The feature which this case brings out beautifully is incipient cirrhosis formation. We saw connections of parenchymal fibrosis with perilobular fibrosis and from the perilobular fibrosis beginning connections between portal veins and hepatic veins. A few nodules were starting to form. We have called this lesion "florid cirrhosis" (1). In Chicago we collected thirty such cases in a relatively short time, and our first publication was based on these cases. All of them had leukocytosis and evidence of cholestasis. Quite a few went to surgery with the wrong diagnosis. If this patient lived long enough, he would have had a fully developed picture of cirrhosis.

This case, I think, has practical importance and was selected primarily be-

cause we do not see many of this type of cirrhosis in this hospital. It is much more common in city institutions with large numbers of "Skid Row" patients.

In trying to correlate the features of the case, first, the patient was an alcoholic for thirty years. I do not know the cause of the jaundice 40, 32 and 18 years before death, obviously starting before the alcoholism. It was not hemolytic. Whether it was Dubin-Johnson's syndrome, I cannot say because we know that when a patient with Dubin-Johnson's syndrome has hepatitis, he loses his pigment. I saw one case where that was quite clearly shown. Whether this patient lost his pigment, I cannot tell. He did have fatty metamorphosis of the liver, hepatomegaly, testicular atrophy, and then, nine months before death, a specific form of hepatic necrosis related to alcoholism, with Mallory's hyaline bodies, high alkaline phosphatase, marked leukocytosis and a little hypoalbuminemia.

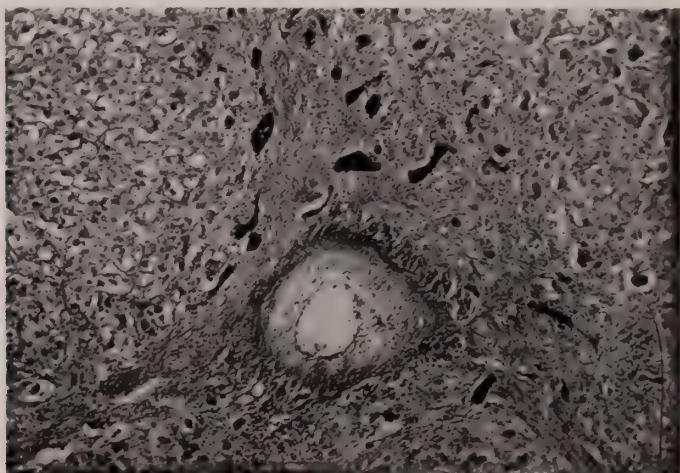


FIG. 8. Endophlebitis with beginning obstruction of hepatic vein branches. (Masson $\times 63$)

The hepatic necrosis led to pericellular fibrosis, ductular proliferation and periductular fibrosis. The hyaline and fat produced some irritation and the result was diffuse hepatic fibrosis. This characteristic feature is not seen in viral hepatitis which we are able to diagnose quite easily in liver biopsy specimens.

The term "florid cirrhosis," which may not be a good one, indicates that the liver injury was very actively progressing into cirrhosis.

The cause of death, I think, is hepatic failure. We found early portal hypertension with just a little splenomegaly, which explains the hyperplasia. I think the hemorrhage was from the stomach.

In closing, this was a case of subacute hepatic necrosis from alcoholism just passing over into cirrhosis. This always represents a difficult clinical problem.

From the floor: Have lesions resembling this even been produced experimentally with alcohol?

Dr. Popper: No. In the experimental animal there is a protracted fatty metamorphosis which does not lead to necrosis.

From the floor: In the cases which you originally described, how frequently was associated pancreatic disease demonstrated?

Dr. Popper: Fairly frequently. I do not remember the figure but I would guess twenty or thirty per cent showed fat necrosis at autopsy.

From the floor: Would you think this man was drinking again in the ten days before death? He was much improved clinically when he left the hospital earlier.

Dr. Popper: Probably. There are two points I cannot clear up. I do not know to what the pleurisy on the left side was due, or what was the cause of the hepatic breakdown. Sometimes patients go for a long time with fatty metamorphosis and then they get the necrosis, usually for one of the following reasons:

1. Infection, which we did not find here.

2. Hemorrhage, which was not profuse enough to explain this.

3. After strenuous or protracted diuresis. You know more than I do about the electrolyte imbalance from release of ascitic fluid, not only by paracentesis but also by diuresis. When I was young, we were told: Do not take too much fluid out, remove it by mercurials. I have learned in the meantime that use of very active diuretics of any kind results in acute electrolyte imbalance which will lead to hepatic failure.

From the floor: On the ward we were very careful not to give the patient diuretics because of the paroxysmal tachycardia, but when he came back the second time he did have hypokalemia.

Dr. Gutman: That might have been a contributing factor. One thing I do not understand is the long duration of jaundice. The changes you have shown us are rather recent. Would they date back six or eight months?

Dr. Popper: Yes. In alcoholics we differentiate two types of lesions. One is florid cirrhosis of this type in which the average duration of the jaundice happened to be nine months. In contrast, in acute hepatic failure of the alcoholic, jaundice is present for an average of three weeks. These patients have very large livers with much fat. The patients with florid cirrhosis have a normal sized liver with regressing fatty metamorphosis.

Final Diagnosis: FLORID ALCOHOLIC CIRRHOSIS.

ADDENDUM

Since this conference was held in 1959, increasing interest and awareness of the broad spectrum of alcoholic liver disease has been manifest. Cholestasis may be present before or at any time during the development of cirrhosis sometimes associated with mild hemolysis (1-3). Hepatic failure may also supervene at any time. Thus, alcoholic liver disease has been considered a single entity, the fatty liver-cirrhosis syndrome, with variable clinical and laboratory findings depending upon the degree of cholestasis, liver cell damage, mesenchymal reaction, and fibrosis (4).

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Radiological Notes

BERNARD S. WOLF, M.D.

New York, N. Y.

CASE NO. 157

This was the second admission to The Mount Sinai Hospital of a 9½ year old girl for evaluation of a cardiac murmur. This murmur had been noted at the age of one month. The child had been in good health since birth, was well developed and weighed 104 pounds. There was no limitation of physical activity. However, the mother felt that this child tired more easily than a twin sister

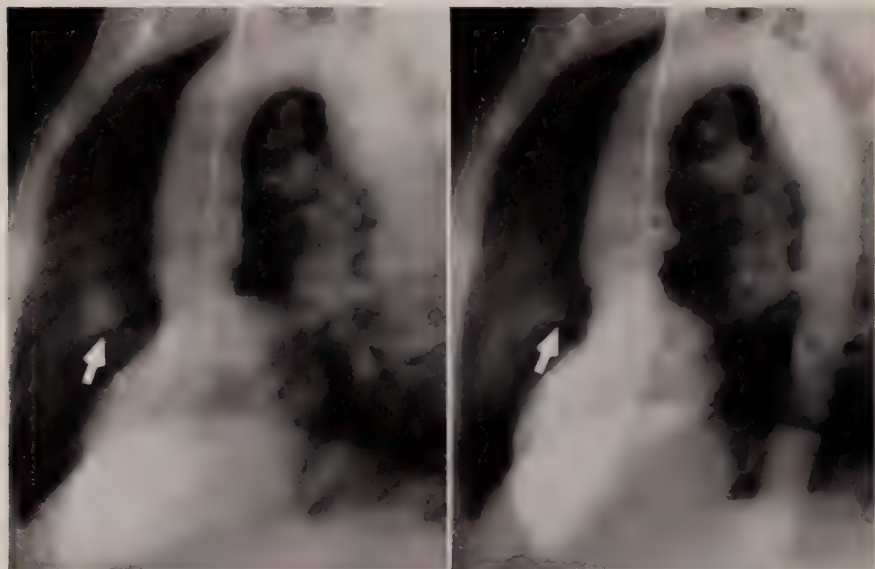


Case 157, Fig. 1. Examination of the chest shows a globular configuration of the heart with no definite evidence of isolated chamber enlargement or significant increase in the transverse diameter of the heart. The main pulmonic artery, hilar and peripheral vessels are not prominent. The aortic knob is not clearly delineated.

who had no evidence of any cardiac disorder. Prior admission to this hospital was one year previously for evaluation of cardiac status. The tentative diagnosis was a ventricular septal defect. Physical examination was negative except for a grade II to III holosystolic harsh murmur loudest in the 4th intercostal space to the left of the sternum. Electrocardiogram was within normal limits. Roentgen examination of the chest (Fig. 1) showed no definite increase in the transverse diameter of the heart or of any specific cardiac chamber. Cardiac

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

configuration was somewhat globular. The pulmonic artery, hilar or peripheral pulmonic vessels were not prominent. The aortic knob was not clearly delineated in the PA projection. Cardiac catheterization during the first admission with complete studies of the right side of the heart and pulmonary artery showed no abnormalities in pressure or oxygen saturation. Efforts to demonstrate a septal defect by dye dilution tests, repeated five times, showed no evidence of a shunt. The patient was readmitted for left side angiocardiology. This was performed



Case 157, Fig. 2A. A lateral film at the beginning of systole taken during left sided angiocardiology performed through a catheter passed into the left ventricle (1) shows a narrow jet of opaque material (arrow) extending from the outflow tract of the left ventricle into the right ventricle.

Case 157, Fig. 2B. Film taken $\frac{1}{6}$ of a second after Fig. 2A shows the jet somewhat more distinctly (arrow). The interventricular defect is located a short distance below the level of the aortic valvular leaflets. The aortic valve leaflets are normal.

via a catheter passed through the right brachial artery. The left ventricle was entered with ease using a catheter with a J-shaped tip. Serial biplane filming was done at the rate of six films per second in each plane. During a systolic contraction (Figs. 2A, 2B), a small jet of opaque material was clearly demonstrated in the lateral projection extending from the outflow tract of the left ventricle into the right ventricle. This jet was seen during successive systoles and was not present during diastole. The opening in the interventricular septum appeared to be about 3 or 4 mm in its maximum diameter. There was no evidence of a valvular deformity.

Catheterization and angiocardiology of the left side of the heart has become a routine procedure when indicated and appears to carry no greater and

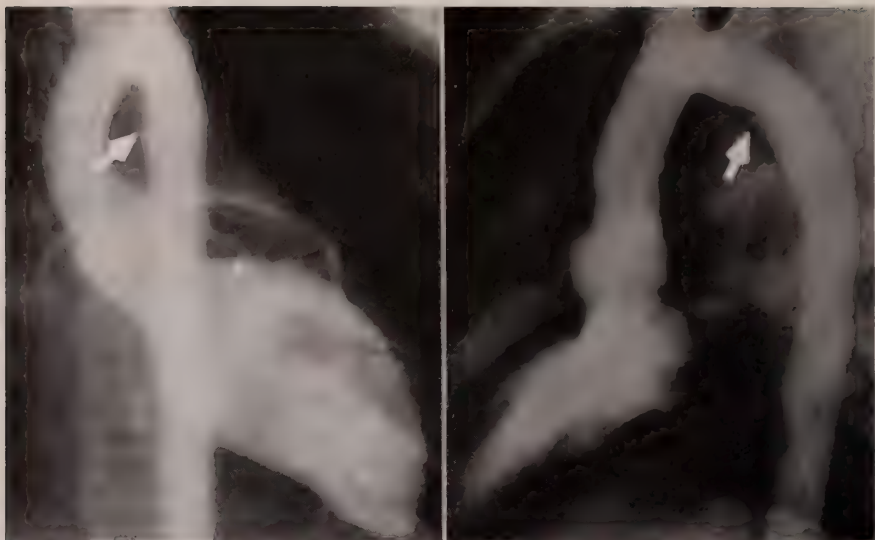
perhaps less hazard than similar studies of the right side. The case presented is of interest because other accepted methods of demonstrating an interventricular septal defect were unsuccessful. Angiocardiography showed not only the presence of a defect but indicated its location and size.

The patient was discharged to be followed in the Out-Patient Department.

Case Report: SMALL INTERVENTRICULAR SEPTAL DEFECT DEMONSTRATED BY LEFT SIDED ANGIOCARDIOGRAPHY AFTER FAILURE OF DYE DILUTION TESTS.

CASE NO. 158

A 9 year old child was admitted to the hospital for investigation of the significance of a heart murmur discovered five years previously. There was no diminution in physical activity, cyanosis or other evidence of cardiac disease. Five years prior to admission, the patient had a single generalized convulsion and had been placed on anticonvulsant therapy. With this, he remained free of seizures. Therapy was stopped after two years and seizures did not recur. Electroencephalogram, however, was abnormal without definite evidence of a focal lesion. Two siblings were alive and well. Examination of the child was not remarkable except for the presence of a grade III systolic murmur along the left sternal border radiating to the apex. There was no abnormal splitting of the pulmonic second sound and no thrill. Electrocardiogram was within normal limits as were films of the chest. Hemoglobin was 11 to 12 gm with a normal white blood count. The tentative diagnosis was a small interventricular septal defect. Catheterization of the right side of the heart showed no evidence of a left to right shunt by oxygen determinations. There was a pressure gradient between the right ventricle and the pulmonary artery across the pulmonic valve of about 20 mm of mercury. The systolic pressure in the right ventricle was 40 mm of mercury and 19 in the proximal portion of the main pulmonic artery. Catheterization data were compatible with the diagnosis of a mild valvular pulmonic stenosis. It was felt, however, that the possibility of an interventricular defect of small size had not been completely excluded. Left sided catheterization was therefore performed with a number 7 J-shaped catheter introduced into the left brachial artery and advanced through the aorta into the left ventricle. Under intravenous pentothal anesthesia, biplane angiocardiography was done (Figs. 1A, 1B, 1C). There was no evidence of an interventricular shunt or abnormality in the aortic valve. However, arising from the anterior aspect of the distal portion of the arch of the aorta, a small funnel-shaped or triangular projection was opacified. This did not have the appearance of an arterial branch. Because of its location and diverticular appearance, the possibility of a patent ductus arteriosus was suggested. In the AP projection, slight infundibular widening was evident. There was no definite evidence of opaque material in the pulmonic artery. It was therefore felt that there was not sufficient evidence to warrant the diagnosis of patency of a persistent ductus but that the diverticular-like projection represented partial persistence of this structure with essentially complete obliteration on the pulmonic side. If this is true, this type of case is



Case 158, Fig. 1A. Left sided angiocardiology in the AP projection shows only slight widening (arrow) in the distal portion of the aortic arch. The catheter extends into the left ventricle.

Case 158, Fig. 1B. In the lateral projection, a funnel-shaped outpouching (arrow) is present on the anterior aspect of the distal aortic arch. The location, direction and configuration of this "diverticulum" suggests that it represents the ductus arteriosus. However, there was no opacification evident in the pulmonary artery or its branches.



Case 158, Fig. 1C. Enlarged view of the aortic side of the ductus arteriosus (arrow).

related to the more common condition of partial persistence of the ductus on its pulmonic side (1). On right sided angiocardiology, this appears as a small diverticular projection from the bifurcation of the pulmonic artery. This is illustrated (Fig. 2) in another patient with a tetralogy of Fallot.

The child was discharged to be followed in the clinic since it was felt that the pulmonic stenosis was minimal.



"Case 158," Fig. 2. Another patient. Demonstration in an infant with the tetralogy of Fallot of partial persistence (arrow) of the pulmonic side of a ductus arteriosus.

Case Report: PARTIAL PERSISTENCE OF THE DUCTUS ARTERIOSUS ON THE AORTIC SIDE.

REFERENCE

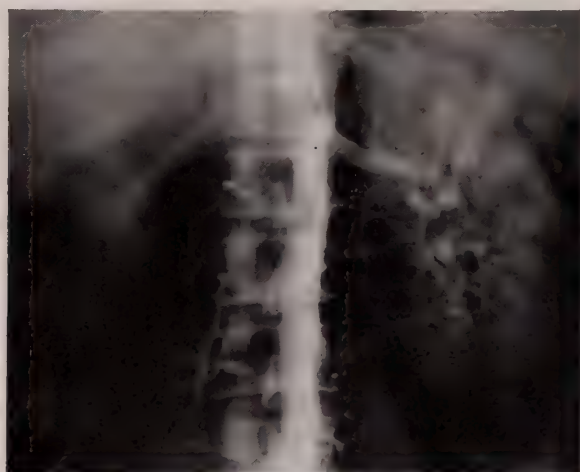
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CASE NO. 159

This was the first admission to this hospital of a 42 year old male with the chief complaint of right costovertebral and flank pain of five days duration. The pain was colicky in nature and sometimes radiated into the anterior aspect of the right thigh. At the outset, the patient vomited, then felt feverish but did not take his temperature. He visited a physician who discovered pyuria and hematuria and was referred to the Emergency Room. An intravenous pyelogram was done and showed no visualization of the right kidney (Fig. 1). An opaque calculus was not seen. The left kidney appeared unusually large. The outline of the right kidney could not be identified. The patient was admitted



Case 159, Fig. 1. Intravenous pyelography shows no evidence of a kidney on the right side. The left kidney is large. The left ureter does not appear remarkable. There is no evidence of an opaque calculus.



Case 159, Fig. 2. Lumbar aortography via a catheter passed percutaneously through the femoral artery confirms the presence of a large left kidney with a large left renal artery. There is no evidence of a right kidney or of a right renal artery. On the right side of the aorta at the level of the left renal artery, there is a flat convex indentation the nature of which is not clear.

for further investigation. Temperature on admission was normal as were other vital signs. Physical examination showed only mild tenderness to deep pressure in the right lower quadrant. There was no costovertebral angle punch tenderness. A small right inguinal hernia was present. The prostate was not enlarged. Hemoglobin was 16.5 mg, red blood count 5 million, white blood count 16,500 with 77 per cent polymorphonuclear leukocytes. The urine was loaded with red



Case 159, Fig. 3. Right vasogram shows the ductus deferens to have a normal caliber and course. The seminal vesicle on the right is obviously distended in irregular fashion and cystic. Joining the seminal vesicle and ascending upwards in the usual position of the right ureter, there is a tortuous tubular structure. There is no evidence of filling of a pelvis or calyces on the right side.

cells and white cells. Cystoscopy demonstrated marked elevation of the right side of the trigone. The right ureteral orifice could not be found. The left was not remarkable. Indigo carmine was seen to come from the left orifice but none appeared on the right side. The region of the trigone looked edematous but biopsy of this area showed only fragments of bladder mucosa with chronic inflammation.

The patient's pain subsided within two or three days on symptomatic therapy. An attempt to demonstrate a right kidney by retrorectal air injection was unsuccessful. Aortography by retrograde percutaneous passage of a catheter through the right femoral artery into the aorta was performed. This confirmed

the fact that the left kidney and the left renal artery were unusually large. A right renal artery or a right kidney could not be identified. In view of the clinical picture of right sided colic, it was deemed advisable to make every effort to recognize the presence or absence of a ureter on the right side. An attempt to inject opaque material into the seminal vesicles via the ejaculatory ducts was unsuccessful. Opaque material was then injected into the right vas deferens in the scrotum. This procedure demonstrated that the right seminal vesicle was enlarged and cystic. Moreover, extending from the seminal vesicle upward in the usual position of the right ureter, a tortuous, somewhat dilated, tubular structure was seen which had the appearance of a ureter. No pelvis and calyces were visualized at the upper end of this structure. It was felt that the patient had an aberrant right ureter entering the seminal vesicle or ejaculatory duct on the right side with an absence or an aplasia of the right kidney. This combination of anomalies has been previously reported in several instances. The patient was therefore explored. By careful dissection, it was possible to remove the right ureter with the seminal vesicle. There was grossly no evidence of a kidney on the right side. The ureter was rather markedly dilated and 24 cm in length in the resected specimen. The wall of the ureter was thickened and the mucosal surface showed numerous valve-like ridges. At the upper end of the ureter, the lumen terminated in a small mass of firm tannish tissue. On microscopic examination, this tissue showed several renal tubules. At the lower end, the ureter opened into a thin-walled hemorrhagic sac about 2 cm in diameter. Within or surrounding this sac there were several small segments of tissue which showed, on microscopic examination, the structure of seminal vesicle. There were several small cavities within the seminal vesicle in one of which a few small stones were found. Four centimeters of the distal portion of the vas deferens were included in the specimen.

The combination of an aberrant ureter and essentially absent right kidney as in this case may be a source of considerable diagnostic difficulty because of difficulty in demonstrating the abnormal anatomical relationships preoperatively. In the case presented, vasography was most useful in demonstrating the nature of the lesion.

Case Report: ABERRANT URETER WITH ABSENT RIGHT KIDNEY—A DIAGNOSTIC PROBLEM.

CASE NO. 160

This was the first admission to this hospital of a 43 year old female with the chief complaint of midepigastriaic pain for two or three years. Originally the pain apparently had a seasonal variation and was worse in the summer time. The patient also stated that the pain ordinarily increased during the night and often was present before eating. The pain was not relieved by eating or drinking milk. The patient claimed that belching was also an annoying symptom. The pain would occasionally radiate around the left side to the back and on occasion to the left lower quadrant. In the past year or two, the pain had become more

persistent. It occurred in the morning and in the afternoon as well as at night and had lost any seasonal variation. About a year before admission to this hospital, the patient was hospitalized elsewhere. Oral and intravenous cholangiogram showed failure to visualize the gallbladder. No opaque stones were demonstrated. Barium meal examination at that time was reported as showing "hypertrophy of the mucosa in the periantral region." A 4+ Wasserman was also found and antiluetic therapy was administered. Seven years before admission



Case 160, Fig. 1A. Barium meal examination shows the prepyloric portion of the stomach over a distance of about an inch to an inch and a half to be narrowed with a hazy somewhat irregular mucosal pattern. The base of the bulb (between arrows) is not deformed. The narrowed segment is rather sharply demarcated from the more proximal distensible portion of the stomach but there is no evidence of an intraluminal filling defect.

she had undergone an operation for an ectopic pregnancy. Appendectomy and left salpingo-oophorectomy were performed at that time.

For a period of two weeks prior to admission, the patient complained of increased pain and was awakened early in the morning with nausea and vomiting. The vomitus consisted of the supper eaten the night before and was yellowish and sour. There was no history of hematemesis or tarry stools. She had lost about eight pounds in weight in the previous two months.

Examination on admission showed some tenderness in the region of the left epigastrium with a sensation of fullness to palpation. The lower edge of the liver was felt two fingerbreadths below the costal margin. There were no other pertinent physical findings. The hemoglobin was 12.7 Gm, white blood count

10.600 with a normal differential count. Wasserman was positive. The stool showed a positive guaiac test on three occasions, negative on one occasion. Gastric analysis with histamine showed free acid up to 44 units and a total acid of 63 units. There was no blood in the gastric aspirate.



Case 160, Fig. 1B. Polygraph from the same examination shows the prepyloric narrowing to be constant and stereotyped. The fairly abrupt step-like junction along the greater curvature with the proximal portion of the stomach appears fixed.

Barium meal examination (Figs. 1A, 1B) showed a great deal of secretion in a distended stomach. The prepyloric portion of the stomach was constantly and somewhat irregularly narrowed with effaced mucosal pattern. The base of the duodenal bulb was intact and the duodenal bulb itself showed no characteristic deformity or evidence of ulceration. There was some delay in gastric emptying. The impression was that a prepyloric carcinoma could not be ex-

cluded. Laparotomy was therefore performed. The prepyloric portion of the stomach was thickened on palpation but there was no evidence of a discrete mass. A subtotal gastrectomy was performed. The removed specimen measured 5 cm along the lesser curvature and 12.5 cm along the greater curvature. The mucosal surface was not remarkable. In the pyloric portion of the stomach, the muscular coat was markedly thickened up to 8 mm whereas elsewhere the muscularis propria was of normal thickness, approximately 2 mm. Many small shotty lymph nodes were present which were microscopically normal. The report was "hypertrophy of the pyloric musculature." There was no evidence of tumor.

The case presented is an instance of so-called idiopathic pyloric stenosis in the adult and demonstrates the great difficulty in differentiating this condition from a scirrhus carcinoma. In some cases of this type in which the muscular hypertrophy is more discrete and localized to the pyloric region and shows on roentgen examination a notch demarcating the thickened muscle from the remainder of the stomach and an "umbrella" defect at the base of the bulb, the correct diagnosis can be suspected. In most cases, this condition is chronic and may not give rise to symptoms sufficiently severe to warrant operative intervention. In the case presented, however, there was both clinical and roentgen evidence of pyloric obstruction of moderate degree. The etiology of this condition is unknown. In some cases, the suspicion exists that the muscular hypertrophy is the result of a gastric ulcer which has healed. In others, as in the current case, there is no evidence of previous ulceration or of a healed scar in the specimen.

Case Report: IDIOPATHIC PYLORIC HYPERTROPHY IN THE ADULT.

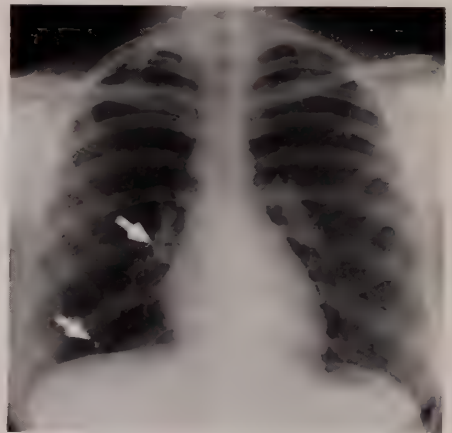
CASE NO. 161

This was the third admission of a 21 year old female with the chief complaints of fever, chills and right pleuritic pain of five days duration. The first admission was two and one half years previously, the second about six months previously, and the story and hospital course on each occasion were identical. In each episode, there was an acute picture of pneumonitis of the right lower lobe which subsided rather promptly over a period of about five days with antibiotic therapy. On the first admission, roentgen examination of the chest (Fig. 1) demonstrated consolidation in the postero-basal and lateral-basal portions of the right lower lobe. Re-examination of the chest (Fig. 2) about six months after subsidence of this episode showed no definite evidence of infiltration, but there was a large calcified node in the right hilum and another calcified node deep in the mediastinum as well as a small calcific focus at the right base. The patient showed a negative tuberculin test but a positive histoplasmin test and it was believed that the calcifications were the result of histoplasmosis since the patient was a native of the middle West. The patient had no significant complaints between episodes except that she stated that she seemed to have somewhat more difficulty in holding her breath during swimming. The roentgen findings of the chest in the second and in the third or current admission were identical, showing evidence of con-

solidation in the postero-basal and lateral-basal segments (Fig. 3). Because of the history of recurring pneumonia in the same segments, the possibility that these were the result of bronchial obstruction was suggested. The roentgen findings suggested that this might be due to broncholithiasis but the age of the patient appeared to favor a bronchial adenoma. On the third admission, a wheeze was audible over the right lower lobe during subsidence of the acute infection. Bronchoscopy was performed and a granular mulberry-like mass about 5 or 6 mm in diameter was found in relationship to the origin of the basal bronchi. Around and behind this mass, thin yellowish-white purulent secretion exuded.

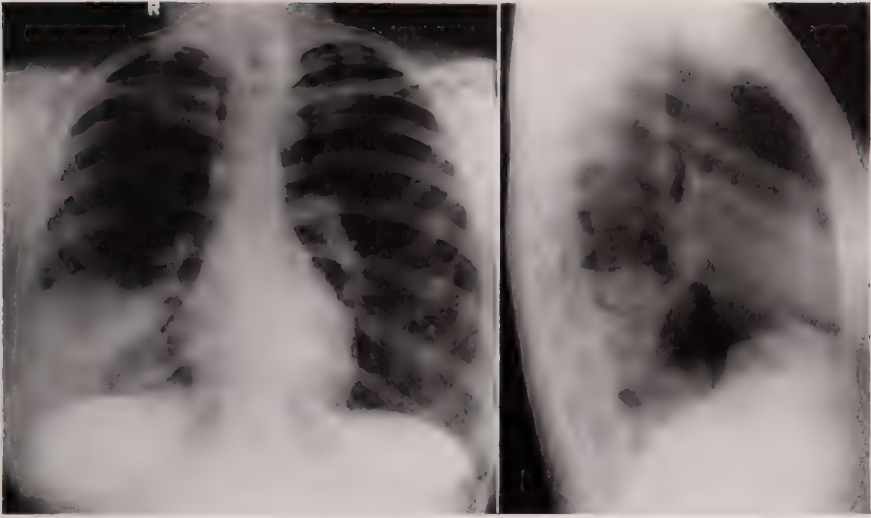


Case 161, Fig. 1. Chest film taken on patient's first admission shows a wedge-shaped area of consolidation in the right lower lobe,—lateral and posterior basal segments. The remainder of the lungs is not remarkable.



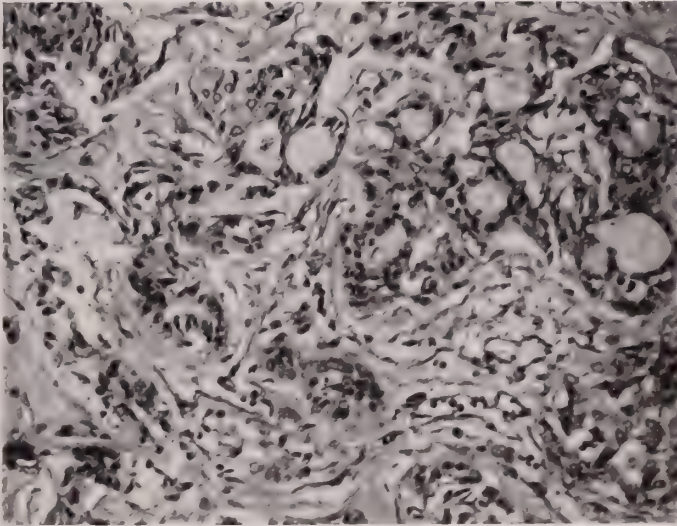
Case 161, Fig. 2. Chest film during asymptomatic interval shows a small calcific focus at the base of the right lung (lower arrow), a large calcified node in the lower portion of the right hilum (upper arrow) and another large calcified node faintly seen in the mediastinum. There is no evidence of infiltration, emphysema or atelectasis in the right lower lobe.

Multiple biopsies were taken. The tissue appeared to be quite friable and soft. It was the impression of the bronchoscopist that the mass was sessile and not pedunculated and could not be removed completely by bronchoscopy without causing undue bleeding. The day after bronchoscopy, the patient coughed up considerable sputum in which an additional piece of tissue was found. Microscopic examination of this tissue as well as the bronchoscopic biopsies (Fig. 4) showed "fragments of bronchial adenoma, mucus producing submucosal gland origin." Two weeks after the original bronchoscopy, a repeat bronchoscopy was performed. On the lateral wall of the right lower lobe bronchus immediately above the lateral-basal branch, there was membrane adherent to the mucosa but the surface was smooth and clean and there was no evidence of neoplasm. No secretion was present and a biopsy was not performed. The patient was dis-



Case 161, Fig. 3A. Posterior-anterior view of the chest is essentially identical to Fig. 1

Case 161, Fig. 3B. Lateral view indicates segmental nature of consolidation. The antero-basal and superior segments are clear.



Case 161, Fig. 4. Photograph of biopsy specimen shows adenomatous structure with numerous goblet cells and cystically dilated glands containing mucus.

charged for further follow-up. Two months after discharge, the patient was bronchoscoped for a third time and there was no evidence of tumor. The patient has been entirely asymptomatic for six months.

This case is of interest because it is an example of a true adenoma arising from bronchial mucous glands. Only seven such cases have been reported in the litera-

ture (1). The majority of so-called bronchial adenomas are either carcinoids, with or without excessive serotonin production, or analogues of salivary gland tumors, specifically cylindroma. The term "bronchial adenoma," while in common usage for all three varieties, theoretically should be confined to the true adenoma.

Case Report: TRUE BRONCHIAL ADENOMA ARISING FROM THE MUCOUS CELLS OF THE BRONCHIAL GLANDS.

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ERRATUM

There was a printer's error on page i (the volume title page) in the November-December 1961 issue. There the volume number for 1961 was given as XXVII. The proper number is XXVIII.

PATTERNS OF BONE CHANGE IN THE ANEMIAS*

JOHN E. MOSELEY, M.D.

New York, N. Y.

CONGENITAL APLASTIC ANEMIA WITH MULTIPLE CONGENITAL ANOMALIES

(Fanconi Syndrome)

In recent years there has been an increasing interest in the hereditary and fetal environmental factors which may result in congenital anomalies. The hematopoietic system is not uncommonly affected by these factors. In addition to the well-known hereditary blood diseases there is an interesting group of hematologic disorders which occur in association with congenital anomalies of other systems. Those that are perhaps best known include congenital leukemia and mongolism, congenital aplastic anemia with multiple congenital anomalies (Fanconi syndrome), congenital spherocytosis associated with congenital hypoplastic thrombocytopenia and malformations and congenital labile factor deficiency with syndactylism. In these conditions bone abnormalities are not the result of the blood dyscrasia but coexist with it. From the point of view of roentgen diagnosis the most important of these is the Fanconi syndrome. In this condition certain bone anomalies occur with sufficient frequency to arouse suspicion of the disorder when they are observed. Added importance may be attributed to these bone defects since the hematologic manifestations of the syndrome do not appear until some years after birth.

The congenital aplastic anemias are divided into two distinct syndromes. In one, the Fanconi syndrome, the idiopathic aplastic anemia is associated with multiple congenital malformations. In the other, there are no associated congenital anomalies. Fanconi's syndrome is characterized by pancytopenia, bone marrow hypoplasia and a variety of congenital anomalies and is the more frequently occurring of the two syndromes. The exact etiology of the condition is unknown but it is generally considered to be hereditary and transmitted by an autosomal recessive gene with variable penetrance. Sporadic cases are seen and at present are thought to be due to spontaneous gene mutation. There is a high familial incidence, several siblings being affected in a number of instances. Fanconi (1) originally described the syndrome in three brothers. On some occasions siblings of patients with the complete syndrome have had congenital anomalies without the hematologic disorder. There does not appear to be any racial or geographic preponderance. The anemia is normocytic and slightly macrocytic and coexists with leukopenia and thrombocytopenia. The leukopenia

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

* The sickle cell states were described in a previous article of this series, and bone changes in the thalassemias will be discussed in a subsequent communication.

is usually due to neutropenia but in some instances all varieties of leukocytes may be affected equally. As in patients with aplastic anemia, the bone marrow varies from acellular to hypercellular.

The number and severity of associated congenital anomalies vary considerably. The most frequent abnormalities encountered are a patchy brown pig-



FIG. 1. Fanconi Syndrome. Hands of 4 year old male with aplastic anemia (pancytopenia) of one month's duration. The patient was small in stature, with a small head and microphthalmia. The testicles were unusually small and there was ptosis of the left kidney. While he was under observation in the hospital, numerous areas of brown pigmentation of the skin developed. There was webbing of the second and third toes bilaterally. Skeletal survey showed hypoplasia of the phalanges of both thumbs and of both first metacarpals. There was a congenital dislocation of the left hip.

mentation of the skin due to a deposition of melanin, dwarfism, hypogenitalism, microcephaly, strabismus, mental retardation, renal and skeletal anomalies.

Skeletal anomalies may be quite prominent in Fanconi's syndrome and outstanding among these are anomalies of the thumbs, first metacarpals and radii. These may vary from complete absence to various degrees of hypoplasia (Fig. 1). Other skeletal abnormalities which have been observed in this syndrome include syndactyly, club foot, congenital dislocation of the hip (Fig. 2) and deformities of various long bones. A variety of other anomalies may be found *but the occurrence of anomalies of the thumb, first metacarpal or radius in conjunction with several other congenital defects of the soft and bony parts should arouse suspicion of Fanconi's syndrome.*

Of considerable interest in this disorder is the fact that hematologic abnormalities are not usually detected until the patient is several years old (2). In most of the reported cases the initial hematologic manifestations occurred between four and twelve years of age. One case has been reported in which the onset was observed to be at thirteen months of age and in two brothers symptoms of a blood disorder appeared at the ages of 19 and 20 years respectively (3). Rare cases have been described of a congenital hypoplastic thrombocytopenia with skeletal and cardiac anomalies. These patients usually die within



FIG. 2. Fanconi Syndrome. This is the patient shown in Fig. 1. There is a congenital dislocation of the left hip.

the first weeks or months of life. They may be considered as neonatal equivalents of the Fanconi syndrome (4). A rather high incidence of leukemia in the families of patients with Fanconi's syndrome has been noted (5).

IRON DEFICIENCY ANEMIA

Every so often a significant new finding is reported in a common, much studied disease and one is left wondering why such an observation was not made long before. A recent excellent example of this interesting phenomenon is the detection of skull changes in iron deficiency anemia in infants and children. Although this disorder has been long and extensively studied throughout the world it was not until 1958 that Lie-Injo Luan Eng (6), an Indonesian investigator, first described bone changes in the skull of a 12 year old Indo-

nesian girl who suffered from chronic iron deficiency anemia. The skull changes were similar to those which may be found in the congenital hemolytic anemias as a result of marrow hyperplasia. Although Lie-Injo Luan Eng's communication was the first documented report with illustrations of the bone abnormality, Caffey (7) had already called attention to the occurrence of these bone changes in his classic paper on Cooley's anemia which appeared in 1957. Shahidi and Diamond (8) reported skull changes in three white infants with iron deficiency anemia in 1960 and Britton, Canby and Kohler (9) added a report of five white children with similar findings. In 1961 Moseley (10) reported skull changes in a Puerto Rican boy and later the same year Burko, Mellins and Watson (11) described similar skull lesions in seven Negro children. No doubt numerous similar reports will follow.

In the newborn infant, following an initial stationary period of about a week or ten days, there is a gradual decline in the hemoglobin and red cells in the peripheral blood. This is the result of normal or slightly increased red cell destruction accompanied by relatively inactive erythropoiesis. The drop in the hemoglobin and red cell levels reaches a maximum at about seven weeks in the premature infant and at about two to three months in the full term infant. The period of diminishing blood levels is referred to as physiologic anemia of the newborn (12). When minimum levels are reached, the relative hypoxia and other stimuli initiate active erythropoiesis. Hemoglobin regeneration is accomplished through re-utilization of iron released from destroyed red cells and stored in the tissues during the postnatal drop in hemoglobin. Such regeneration depends primarily, therefore, upon the hemoglobin concentration and hemoglobin mass available at birth. With growth the supply of stored iron is depleted and the infant is exposed to an iron deficiency anemia if the supply is not replenished by an adequate diet. The more rapidly the infant grows, the greater is the strain on the iron supply. According to Smith (12) the most important causative factors in iron deficiency anemia in infants and children are: 1) inadequate iron stores at birth which may result from premature, twin or multiple births, severe iron deficiency in the mother or fetal blood loss at or before delivery; 2) inadequate intake due to a deficient diet; 3) impaired absorption due to gastrointestinal disorders and 4) excessive demands for iron, such as may result from blood loss during infancy or failure to meet increased demands for growth. The factors of inadequate supply and excessive demand for iron tend to be interdependent and overlapping. In the presence of anemia the erythropoietic response is exaggerated and the overactive erythropoiesis is manifested mainly as marrow hyperplasia.

BONE CHANGES IN IRON DEFICIENCY ANEMIA

The skull changes which may be radiographically demonstrated in some cases of iron deficiency anemia in infants and children are similar to those which occur in the congenital hemolytic anemias and are similarly due to erythroid hyperplasia of the diploic marrow between the tables of the skull. The diploic space is widened. The outer table is displaced externally and is often thinned

(Figs. 3-5). In some cases it may be completely atrophied. Occasionally the diploic trabeculae assume a position perpendicular to the inner table presenting a radial pattern which when advanced is referred to as a hair-standing-on-end appearance. Caffey (7) has called attention to the usual absence of involvement

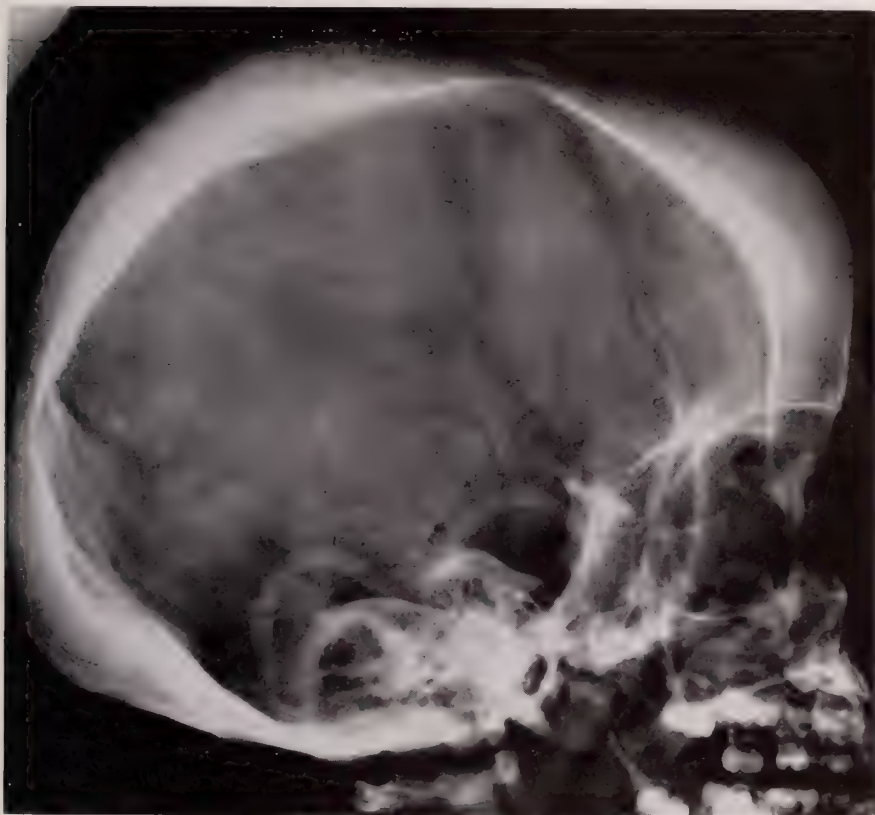


FIG. 3. Iron Deficiency Anemia. The skull of a three year old Puerto Rican male shows widening of the diploic space. The parietal trabeculae show an early fine radial pattern. The outer table is atrophic in some areas and there is a generalized granular osteoporosis. The frontal, parietal and occipital bones are all affected but the occipital squamosa inferior to the internal occipital protuberance is uninvolved, probably because there is normally no marrow in this portion of the bone. This patient was born at term with multiple cutaneous hemangiomata and cerebral vascular anomalies. He was mentally retarded and would take no solid foods. His diet consisted almost solely of milk. There was a prompt response of the anemia to iron therapy. (Moseley, J. E.: *Am. J. Roentgenol. & Rad. Therapy*, 8: 649, 1961.)

of the occipital squamosa inferior to the internal occipital protuberance in cases of hemolytic anemia and this appears to be so in iron deficiency anemia as well. It is presumably due to a normal absence of marrow in this portion of the bone. None of the cases of iron deficiency anemia so far reported have shown swelling of the facial bones with retardation of pneumatization of the maxillary sinuses as occurs in severe Cooley's anemia and no roentgen evidence of marrow hyperplasia has been reported in the long bones. In Cooley's anemia roentgen evidence of marrow hyperplasia is consistently found

in the long and short tubular bones, particularly the metacarpals and distal femora. Changes are often manifest in the extremities when none are present in the skull but skull changes in the absence of tubular bone alterations are not seen in infants and young children. After puberty, when the lesions in the tubercular bones regress, involvement of the central skeletal segments, including the skull may persist and increase. On the

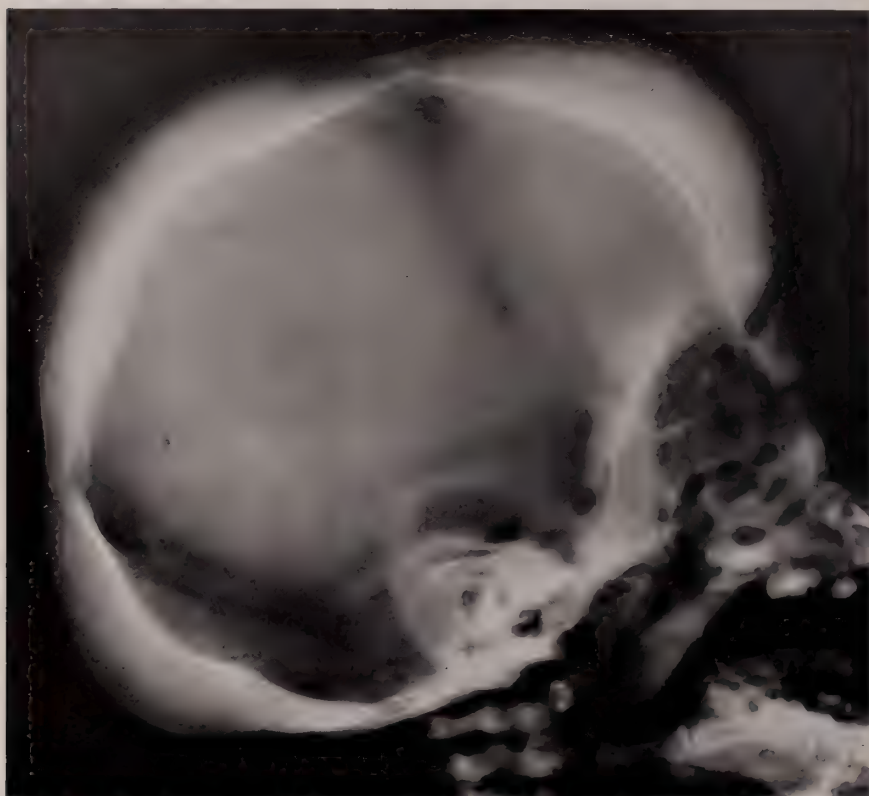


FIG. 4. Iron Deficiency Anemia. Same patient at age 2½ years. The diploic space is widened but radial striation of the trabeculae is not yet apparent. There is no swelling of the facial bones. (Moseley, J. E.: *Am. J. Roentgenol. & Rad. Therapy*, 8: 649, 1961.)

basis of our experience and the descriptions of all cases published to date the absence of facial bone involvement and, more particularly, the absence of long bone changes differentiate the roentgen bone changes of iron deficiency anemia from those of severe Cooley's anemia in infants and young children.

As in the chronic hemolytic anemias there is marked variation in the roentgen findings in the skulls of patients with iron deficiency anemia. Patients of the same age with similar clinical and hematologic findings may show marked differences in the roentgen appearance of the skull. Siblings with iron deficiency anemia as severe or more severe than those with skull changes may show no

cranial bone abnormalities whatsoever. In both chronic hemolytic anemia and in chronic iron deficiency anemia the skull is an unpredictable and unreliable index of the severity of anemia (11).

Of the reported children with iron deficiency anemia and skull changes a large number have been born prematurely or were born with a twin. Many of those born at term were considerably less than average in birth weight. Most of the patients suffered from poor diets which consisted mainly of milk. The 12 year old girl reported by Lie-Injo Luan Eng was said to have had an adequate

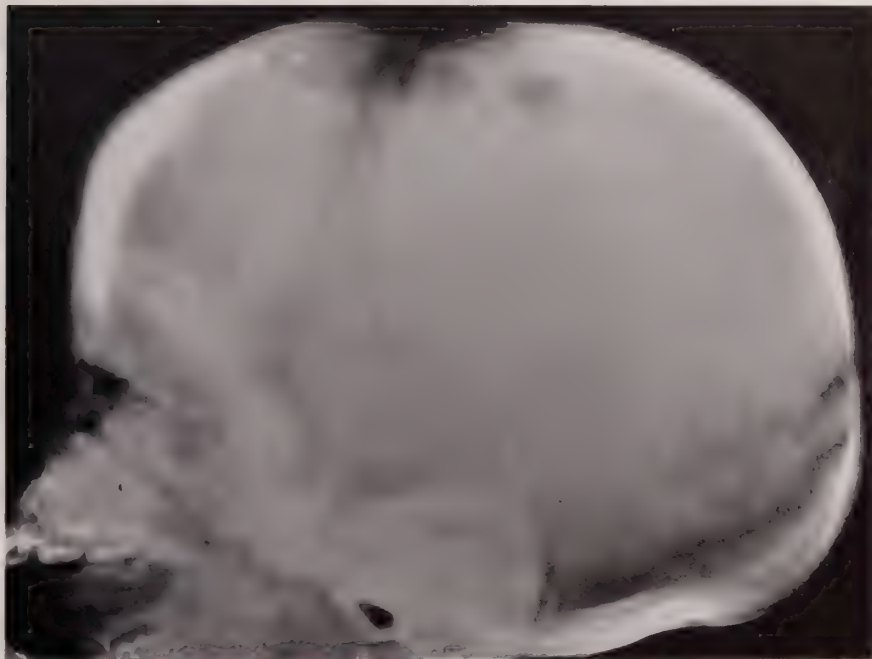


FIG. 5. Iron Deficiency Anemia. Skull of same patient taken at 3 months of age. Early changes are already apparent in the frontal bone. (Moseley, J. E.: *Am. J. Roentgenol. & Rad. Therapy*, 8: 649, 1961.)

diet and the anemia was believed to have resulted from chronic blood loss from the intestinal tract due to hookworm infestation.

Skull changes similar to those occurring in the congenital hemolytic anemias and in iron deficiency anemia have also been reported in other conditions accompanied by erythroid hyperplasia. Ascenzi and Marinozzi (13) have described such skull findings in two girls, age $3\frac{1}{2}$ and 6 years, with cyanotic congenital heart disease and secondary polycythemia. In the $3\frac{1}{2}$ year old child the cardiac malformation was that of pulmonary atresia with an interatrial septal defect. In the 6 year old girl there was a tetralogy of Fallot. At autopsy both skulls showed marked erythroid hyperplasia of the marrow with widening of the diploic space similar to that seen in Cooley's anemia, sickle cell disease, familial hemolytic icterus and iron deficiency anemia. Erythroid hyperplasia

in cyanotic congenital heart disease is due to hypoxemia resulting from the circulatory shunts. Dykstra and Halbertsma (14) have reported skull changes of the same kind in a 12 year old patient with polycythemia vera.

ERYTHROBLASTOSIS FETALIS

(Hemolytic Anemia of the Newborn)

Erythroblastosis fetalis is a hematologic disorder which occurs in the fetus and newborn as a result of excessive destruction of the erythrocytes. Excessive hemolysis leads to active erythropoiesis in the liver, spleen and bone marrow with the frequent appearance of nucleated red cells in the peripheral blood, a circumstance which accounts for the name given to the disease. Excessive destruction of fetal erythrocytes results from the presence of an antigenic factor in the fetal red blood cells which is not present in the red cells of the mother. When this antigenic factor gains entrance into the maternal circulation a specific antibody is developed in the mother. Maternal antibodies recrossing the placenta gain access to the fetal circulation and result in excessive destruction of fetal red cells. The manifestations of erythroblastosis stem from this action of maternal antibodies on fetal red cells prenatally and in the early neonatal period. In erythroblastosis due to Rh incompatibility, fetal Rh positive blood enters the circulation of an Rh negative mother. A similar mechanism may occur due to incompatibility within the ABO groups. The incidence of Rh negative individuals is considered to be much less among Negroes and when erythroblastosis occurs in the Negro, ABO incompatibility is the more common cause. Rh incompatibility is not distinctly uncommon, however, in this racial group.

Erythroblastosis fetalis may be manifested in any one of three clinical forms. These are: 1) congenital anemia; 2) icterus gravis and 3) fetal hydrops. So-called congenital anemia of the newborn and icterus gravis account for about seventy per cent of all cases of hemolytic disease in the newborn. The designations, however, indicate only different degrees of the same pathologic process. Congenital anemia of the newborn is a mild form of the condition in which pallor becomes apparent as jaundice recedes in the first week of life. In icterus gravis neonatorum the disease is more severe and there is progressive anemia and jaundice. In fetal hydrops there is a massive edema of the fetus which is usually stillborn and premature. All three conditions represent different degrees of severity of the hemolytic process.

Bone Changes in Erythroblastosis Fetalis

Nonspecific bone changes may occur in all forms of this hemolytic disorder. Their incidence tends to increase with the severity of the disease. In many cases of both mild and severe disease no bone changes can be demonstrated. The bone lesions are hardly of any real diagnostic significance, however, since they may occur in numerous other disorders of the mother, fetus or infant. When skeletal alterations are demonstrable they consist of transverse bands of diminished and increased density at the metaphyseal ends of long bones, ad-

jacent to the zone of provisional calcification (Fig. 6). These result from interference with prenatal endochondral bone formation and are in no way different from similar bands which may be seen in premature infants, infants born after



FIG. 6. Erythroblastosis Fetalis. There are transverse bands of radiolucency at the ends of the long bones adjacent to the zones of provisional calcification. Adjacent to these are bands of increased density. Similar zones are noted in the round bones of the feet. (Courtesy of Dr. David Baker, New York, N. Y.)

a pregnancy in which there was significant maternal illness, fetal diseases such as congenital syphilis or acute and chronic diseases of infancy. Follis and his associates (15) reported a diffuse sclerosis of the long bones with narrowing of the medullary cavities in this condition in 1942 and many present-day descrip-

tions of erythroblastosis continue to perpetuate this belief (16). Thick cortices with narrow medullary cavities are frequently seen, however, in premature and normal full term newborns and are of no radiologic significance. When present the metaphyseal bands tend to occur most frequently at the sites of most active bone growth and may be best demonstrated at the wrists, knees and ankles. Analogous lines or bands may occur in the round bones and epiphyses as well. These lesions tend to be bilaterally symmetrical and in some cases may be distinct enough to be demonstrable in the fetus *in utero* on films made of the maternal abdomen. If the patient survives, the metaphyseal bands tend to disappear and to be replaced by thin transverse lines of increased density (growth lines) deeper in the shaft, depending on the interval between examinations (17).

HEREDITARY SPHEROCYTOSIS

(Congenital Hemolytic Jaundice)

Hereditary spherocytosis is a genetically determined, chronic hemolytic disease characterized by the presence of spherocytes in the peripheral blood, increased osmotic fragility of the red cells and, commonly, an enlarged spleen. The defect is transmitted by either parent as an autosomal dominant characteristic, males and females being equally affected. Some discrepancies in the hereditary transmission of the disorder have been observed and have been tentatively ascribed to spontaneous mutation or incomplete expressivity of the responsible gene (18). The disease is considered to be relatively rare among Negroes (19).

The genetic defect is responsible for an intrinsic anomaly of the red cell which accounts for its globular shape and increased susceptibility to hemolysis. These spherically shaped cells of abnormal thickness are trapped in the spleen and destroyed more rapidly than normal cells. Splenectomy corrects the anemia in these patients but spherical red cells persist as do their increased osmotic and mechanical fragility (20).

The clinical manifestations of hereditary spherocytosis vary considerably both in regard to the time of onset and their intensity. They are usually first recognized in childhood or adolescence but the onset may occur in infancy or as late as middle age. Jaundice is uncommon in infancy and early childhood but may be present when the disease is manifest in the newborn. In these latter circumstances the condition may simulate erythroblastosis. Jaundice is more apt to appear in late childhood and becomes more pronounced in the young adult. Although the degree of anemia varies, it is seldom severe.

Bone Changes in Hereditary Spherocytosis

The bone changes which may occur in spherocytic anemia are due to the premature destruction of abnormal red cells. Compensatory erythropoiesis results in marrow hyperplasia. Overgrowth of marrow is manifested as expansion of the medullary spaces and atrophy of the spongiosa and cortex. In this disorder,

however, anemia is usually only moderate in comparison to the two other congenital hemolytic anemias associated with bone changes *i.e.*, Mediterranean and sickle cell anemia. On occasion there may be no anemia at all. On the other hand in some instances anemia may actually be severe. Furthermore, as many cases do not become overt until late childhood or adolescence when red marrow is disappearing or has been converted to fatty marrow in the peripheral skeleton,

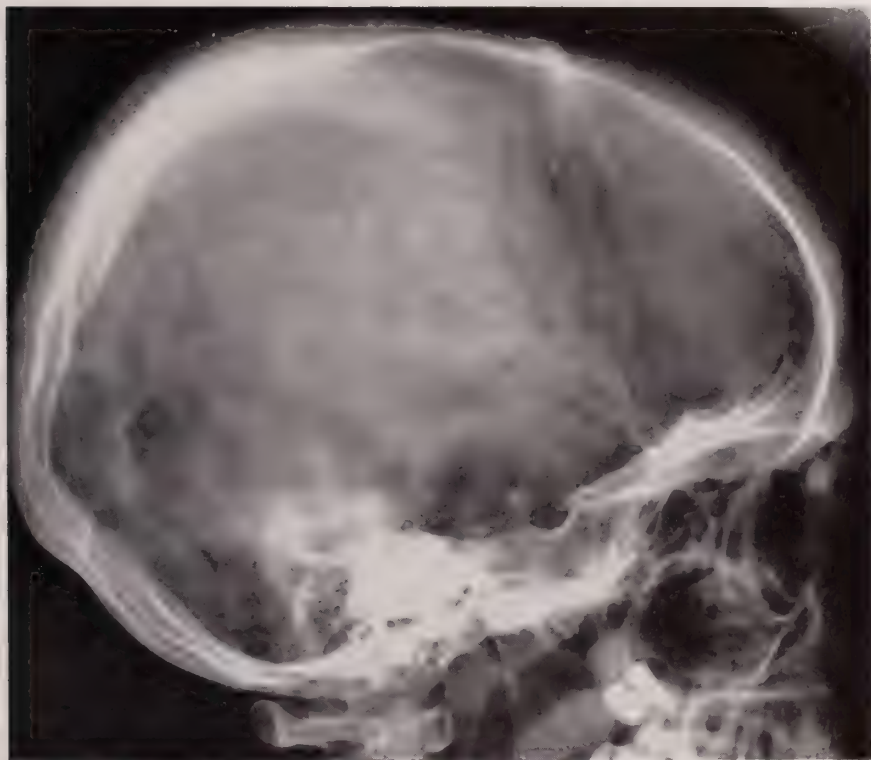


FIG. 7. Hereditary Spherocytosis. Skull of 11 year old patient showing widening of diploic space in the frontal and parietal bones. The trabeculae in the parietal bone are arranged in a perpendicular striated pattern. There is no swelling of the facial bones. (Courtesy of Dr. David Baker, New York, N. Y.)

roentgen evidence of marrow hyperplasia in the tubular bones is distinctly uncommon. Since red marrow persists in the central skeletal segments roentgen signs of erythroid hyperplasia are most apt to be found in these areas when it occurs. The skull is the most frequently involved portion of the skeleton and the bone alterations there, which are similar to those which occur in other conditions as a result of marrow expansion, are distinctly milder and occur less often in spherocytic anemia than in Mediterranean or sickle cell anemia (Fig. 7). In those instances, however, in which the disease occurs with some severity in young children long bone changes may be demonstrated. Improvement in the skeletal alterations following splenectomy has been reported (21).

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ACUTE IDIOPATHIC PERICARDITIS WITH GRANULOMA FORMATION

A CASE REPORT

PHILIP L. HOROWITZ, M.D., AND ALAN B. ECHIKSON, M.D.

New York, N. Y.

There are many causes of the syndrome of acute pericarditis. In many cases, a specific etiology, such as acute rheumatic fever, tuberculosis or fungal infections can be found. In other instances the etiology is more obscure. The latter cases have been grouped under the term "acute idiopathic pericarditis," a disease with a typical clinical course but which is undoubtedly of varied etiology.

"Acute idiopathic pericarditis" was first described by Hodges in 1854 (1). Little attention was paid to this condition until 1942, when the paper by Barnes and Burchell stimulated interest in it (2). The pathology of this disease has been described in only a few instances, apparently because of the rarity of a fatal outcome. With the advent of open pericardial biopsy, pathologic studies have been made in several nonfatal cases. Almost invariably, histologic examination has revealed a nonspecific inflammatory reaction. We wish to present a patient who demonstrated the typical clinical course of "acute idiopathic pericarditis" and in whom granulomatous lesions were found in the pericardium on biopsy. There has been only one other instance that we were able to find in the literature; the case reported by Movitt *et al.* (3), in which similar pathologic findings in this disease were described. We shall also discuss the differential diagnosis of a patient with acute pericarditis and review the various etiologic agents which may be responsible for granulomatous lesions of the pericardium.

CASE REPORT

A.G., a 62 year old Puerto Rican female was admitted to The Mount Sinai Hospital on May 2, 1959. Two weeks prior to admission she had suffered from a mild upper respiratory infection. Four days prior to admission she noted the onset of fever, as high as 104°, and severe substernal and interseapular pain that was pleuropericardial in nature. Her symptoms persisted and were associated with progressive dyspnea, necessitating emergency admission to the hospital at 2 a.m. The patient specifically denied a past history of tuberculosis, rheumatic fever, arthritis, rash, prolonged fever, renal disease, hypertension, previous chest pain or pleurisy.

Physical examination revealed an acutely ill obese female writhing in bed and complaining of severe chest pain. The temperature was 102.6°, the pulse rate was regular at 120/min, respirations were shallow at 40/min and the blood pressure was 110/85 with marked pulsus paradoxus. The cervical veins were distended when the patient was sitting in the upright position. Examination of

From the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

the chest revealed dullness in the left paraspinal area but no bronchial breathing in this region. There were bilateral basilar rales. The heart size could not be determined and the tones were of good quality. No murmurs, rub or gallop could be heard. The liver was enlarged to three finger-breadths below the right costal margin and was moderately tender with marked hepatojugular reflux. There was no splenomegaly, lymphadenopathy, ankle edema or eruptions.

Admission laboratory examinations revealed a normal urinalysis, a hemoglobin of 10.3 Gm per cent and a white blood cell count of 16,650 per cu mm with 70 segmented neutrophils, 15 band forms and 15 lymphocytes. The erythrocyte sedimentation rate was 111 mm per hour. Chest x-ray suggested a "water bottle" cardiac silhouette and revealed small bilateral pleural effusions. Fluoroscopy demonstrated the absence of cardiac pulsations. The electrocardiogram (Fig. 1) showed low voltage of the QRS complexes, elevation of the ST segments in leads I, II, and aVF and depression in aVR, and incomplete right bundle branch block. The venous pressure was greater than 300 mm of water and the decholin circulation time was 18 seconds.

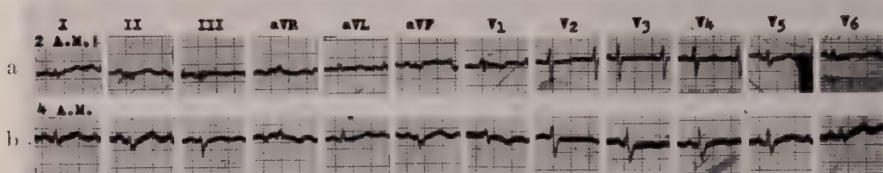


FIG. 1 (a). Electrocardiogram taken on admission before pericardiocentesis.

FIG. 1 (b). Electrocardiogram taken immediately after pericardiocentesis. Note increased voltage of QRS complexes.

During the first two hours of hospitalization evidence of progressively severe cardiac tamponade rapidly developed as manifested by marked dyspnea, diminishing pulse pressure and increasing tachycardia. An emergency pericardiocentesis via a paraxiphoid approach was therefore performed and 325 cc of serosanguineous fluid was removed, and 100 cc of air injected into the pericardial sac. There was dramatic relief of pain and immediate disappearance of signs of tamponade following this procedure, as evidenced by a reduction in the venous pressure to 60 mm of water, an increased QRS voltage on the electrocardiogram (Fig. 1) and disappearance of the paradoxical pulse. X-rays (Fig. 2) revealed a hydropneumopericardium, and the parietal pericardium appeared to be slightly thickened; however, it was smooth and did not reveal any nodularity.

Studies of the pericardial fluid revealed many red blood cells, a total protein of 6.0 Gm per cent, negative cell block for malignant cells and a negative LE preparation. Gram and Ziehl-Nielsen stains and cultures for pyogens, fungi and acid-fast bacilli demonstrated no organisms. The patient's hospital course is summarized in Figure 5.

With a presumptive diagnosis of "acute idiopathic pericarditis" with effusion, and because of the severity of the patient's illness, the patient was started on prednisone, 60 mg per day in divided doses. The next day, a moderately loud

pericardial friction rub was heard along the left sternal border for the first time. This disappeared after three days and was never audible again. Over the next several weeks all signs of cardiac tamponade disappeared. The ppd #1 was negative but intermediate strength ppd was positive. Numerous LE preparations were negative and the antistreptolysin—O titer was 166 units on two occasions. The serum glutamic oxaloacetic transaminase was 31 units. On several determinations, agglutination studies against apc, Coxsackie and influenza vi-



FIG. 2. Chest x-ray taken immediately after pericardiocentesis and introduction of air into pericardial cavity. Note hydropneumopericardium and the smooth outline of the pericardium.

rus were negative, as was the mumps complement fixation test. Serial electrocardiograms revealed increasing voltage of the QRS complexes and the ST segment and T wave changes reverted towards normal. Electrocardiographic evidence of a myocardial infarction never developed.

Additional laboratory studies revealed the blood urea nitrogen to be 10 mg% and the fasting blood sugar 86 mg%. The total protein was 6.5 Gm% with 3.0 Gm of albumin and 3.5 Gm of globulin. The serum sodium was 142 mEq/L, and potassium 4.4, the chloride 104, and the carbon dioxide combining power 27.7 mEq/L. The serum bilirubin was 0.2 mg% and the total cholesterol 138 mg%. The alkaline phosphatase was initially elevated to 16.5 King-Armstrong units

but shortly thereafter fell to 8.5 units and remained in this range. The prothrombin time was 13.5 seconds with a control of 12 seconds. The thymol turbidity was 1 unit and the cephalin flocculation was negative. The serum amylase was 27 units. Numerous blood cultures were negative as were the febrile agglutinins. Serum electrophoresis was normal except for somewhat low gamma globulin. A chest x-ray (Fig. 3) taken five days after admission, still showed an enlarged cardiac silhouette. However, by the 16th hospital day the chest x-ray (Fig. 4) revealed a normal sized heart and clear lung fields, and subsequent chest films taken serially throughout the patient's course were normal. A gall bladder series was negative.

In view of the negative cultures of the pericardial fluid for acid-fast bacilli,

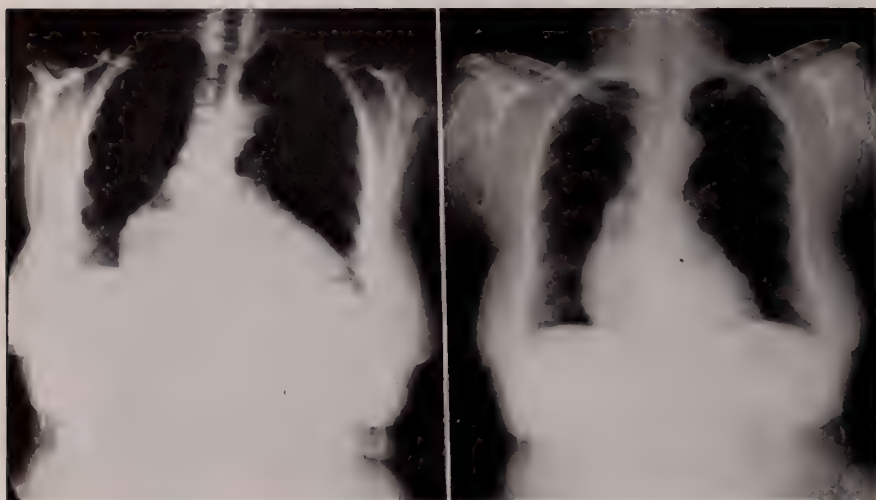


FIG. 3. Chest x-ray taken on the fifth hospital day demonstrating an enlarged cardiac silhouette, with an appearance suggesting fluid in the pericardial space.

FIG. 4. Chest x-ray on the sixteenth hospital day showing a diminution in the size of the cardiac silhouette.

pyogens and fungi, and the negative lupus preparations and ASL-O titers, a diagnosis of "acute idiopathic pericarditis" was made. This impression was further strengthened by the patient's dramatic response to prednisone in the absence of antituberculous chemotherapy and antibiotics. Treatment was prednisone was therefore continued in gradually diminishing dosage, and by the fourteenth hospital day the patient was essentially well. By the nineteenth hospital day the dose of prednisone had been reduced to 10 mg per day. However, on the twenty-first day the patient had a fever of 102° , pleuropericardial pain, a pulsus paradoxus, acute T wave inversions in leads V_1 to V_6 of the electrocardiogram and distant heart tones. Our impression was that the pericarditis had recurred, associated with the decrease in steroid dosage; therefore, the dose of prednisone was increased to 60 mg daily with rapid relief of symptoms. However, leukocytosis and a rapid sedimentation rate persisted, and there were occasional slight elevations in the temperature. Because of these findings

steroid therapy in doses of 60 mg per day was maintained for four weeks. During this period the patient had epigastric distress. An upper gastrointestinal series was taken and revealed a duodenal ulcer, necessitating the institution of an ulcer regimen and gradual reduction in steroid dosage. By the 81st hospital day the patient was taking 20 mg of prednisone per day, when she suddenly suffered a second recurrence of pericarditis. She was again given 60 mg of prednisone daily, with complete symptomatic relief but with persistence of leukocytosis (perhaps secondary to steroid therapy) and an elevated sedimentation rate.

Because of the obscure nature of the illness and the prolonged disability, it was decided to obtain an open pericardial biopsy. Accordingly, on the 108th hospital

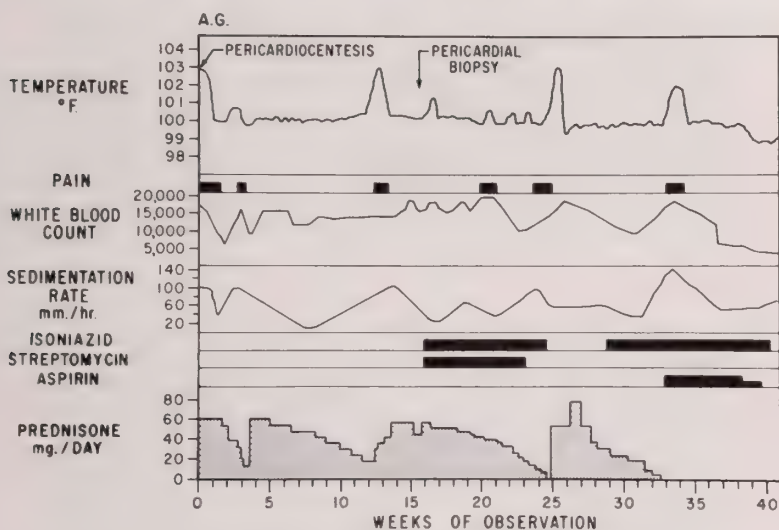


FIG. 5. Chart summarizing the patient's hospital course.

day, after three days of treatment with streptomycin and isoniazid, the patient was taken to the operating room where, under general anesthesia, the chest was entered through the fourth left intercostal space. The pericardium was exposed and appeared slightly thickened. A biopsy of the parietal pericardium was performed and a small quantity of pericardial fluid was obtained for culture. Pathologic sections (Fig. 6) revealed "focal chronic inflammation and epithelioid cell and giant cell granulomata." There was no caseation. Acid-fast bacilli were not recovered from the fluid. The pericardial tissue was also sent for culture but was unfortunately misplaced.

In view of the negative cultures of the pericardial fluid, the acute onset of illness and the dramatic response to steroids alone, it was our belief that the patient did not have tuberculous pericarditis. However, the finding of epithelioid cell granulomatous lesions in the pericardium was a most disturbing feature. Because of our concern over the possibility of tuberculous pericarditis it was deemed best to continue the patient on antituberculous chemotherapy with

isoniazid in doses of 300 mg per day. Prednisone, however, was gradually reduced and by the 120th day was stopped completely.

However, two days later the patient suffered her third clinical relapse with

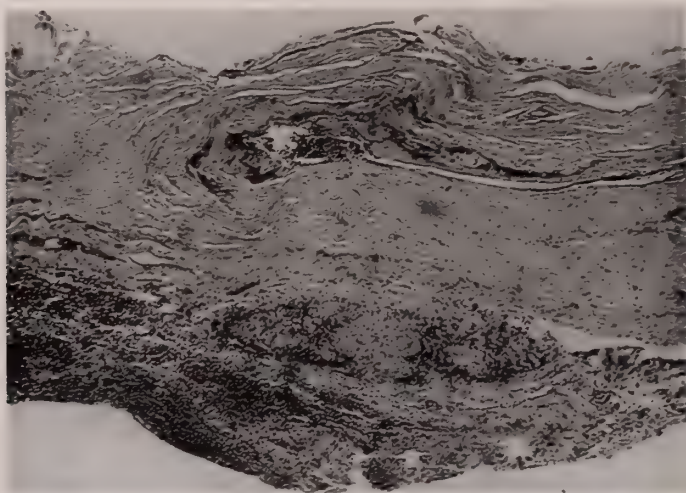


FIG. 6 (a). Section of pericardium ($\times 60$) demonstrating granulomata.

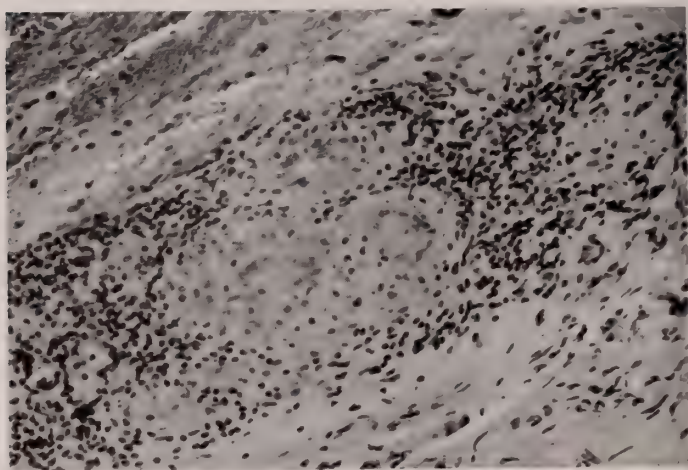


FIG. 6 (b). Higher power magnification ($\times 200$) of a granuloma demonstrating epithelioid and giant cells.

fever and chest pain. She again responded within hours to reinstitution of prednisone in doses of 40 mg per day. After nine days the dosage of prednisone was again reduced, and by the 159th hospital day was stopped completely. The patient was then observed for one week in the hospital, during which time she remained entirely well. At this time a liver biopsy was negative, revealing no granulomata. It was intended to observe the patient for a longer period of

time but at her insistence she was discharged from the hospital on the 166th hospital day, on a regimen of isoniazid 300 mg per day and without steroids.

Two days later (nine days after withdrawal of prednisone) the patient was readmitted to the hospital stating that on the evening of the day of discharge she had fever, chills, and substernal pleuritic pain which then localized to the right lower anterior chest. There was no cough or hemoptysis. On physical examination the temperature was 103.2°, the pulse 130/min. and regular, respirations 20/min., and the blood pressure 150/80. There was a patch of fine rales at the right base posteriorly. The heart was not enlarged, the sounds had a tic tac quality and the rate was 130 per minute and regular. There was no pericardial or pleural friction rub.

Laboratory data revealed a hemoglobin of 12 Gm%, a white blood cell count of 15,000 per cu mm with 51 segmented neutrophils, 30 band forms, 11 lymphocytes, and 8 monocytes. The erythrocyte sedimentation rate was 99 mm per hour. Urinalysis was negative. The venous pressure and decholin circulation time were normal. Blood culture was negative. The electrocardiogram and chest x-ray were unchanged from previous studies; the electrocardiogram revealing nonspecific T wave changes in the precordial leads, (inverted or diphasic T in V₁ to V₄), and the x-ray revealing a normal sized heart and clear lungs. Additional tests included negative coccidioidin blastomycin and histoplasmin skin tests, absence of ova and parasites from the stool and negative Brucella agglutinins. A Nickerson Kveim test was negative as was a Frei test.

It was felt that this episode represented the fourth exacerbation of illness secondary to steroid withdrawal. As a therapeutic trial the patient was given an immediate dose of 30 mg of prednisone. Within four hours there was a dramatic improvement in her condition with marked relief of pain, drop in temperature to 100° and clearing of the lungs. Accordingly she was started on 60 mg of prednisone daily. Once again she did very well except for a persistent elevation of the ESR in the range of 50–80 mm per hour. Because of her proved peptic ulcer, the development of a mild steroid diabetes, and the feeling that steroids might be prolonging her illness, it was decided to make one final attempt to withdraw steroids and treat any exacerbation with salicylates. It was our plan that should this fail to bring the illness to a halt, consideration would then be given to submitting the patient to pericardiectomy. Therefore, prednisone was tapered and on the 49th hospital day it was completely stopped. As we expected, on her fourth day off steroids the patient had a full blown exacerbation of her illness with fever to 102.4°, representing her fifth recurrence since the onset of the disease. She was maintained on antituberculous chemotherapy and started on acetylsalicylic acid, 7.2 grams per day. She gradually responded to this therapy and after ten days of fever and chest pain, became afebrile and asymptomatic. Aspirin was continued for a total of 35 days, gradually tapered and then stopped. Further observation for ten days revealed no recurrence of illness. She was discharged on January 21, 1960, to be followed in the outpatient clinic. When last seen, seven months after discharge, she was entirely well.

To summarize, this patient had acute pericarditis following an upper respiratory infection. The course was complicated by a hemorrhagic effusion with cardiac tamponade which was relieved by pericardiocentesis. Subsequently, the patient had a prompt response to adrenocortical steroids only to suffer five recurrences of her illness, all of which were milder than the original episode. These occurred at periods when steroids had been discontinued or rapidly decreased in dosage. Four of these recurrences responded promptly to reinstitution of large doses of prednisone, and the fifth to salicylate therapy. It should be noted (Fig. 5) that three recrudescences of disease occurred while the patient was being treated with isoniazid. Because of her prolonged illness and in order to clarify the nature of the disease, a pericardial biopsy was performed and revealed non-caseating granulomata. Many further diagnostic studies failed to reveal a specific etiology.

Because our patient's course was typical of "acute idiopathic pericarditis," a search of the literature was undertaken to find if there were any instances of this disease demonstrating granulomatous lesions. We were able to discover only one similar case, that described by Movitt *et al.* (3). We wish, therefore, to present our reasons for believing that this patient had "acute idiopathic pericarditis," and to discuss briefly the previous descriptions of the pathology of this disease and differential diagnosis of a patient with acute pericarditis.

DISCUSSION

"Acute idiopathic pericarditis" is an illness with an abrupt onset, a febrile course and usually an excellent prognosis. It is preceded by a respiratory infection in fifty to eighty per cent of cases (4-6). The history of such an infection, as was obtained from our patient, in the presence of acute pericarditis is strongly suggestive of the diagnosis of "idiopathic pericarditis" (7). The onset of symptoms is typically sudden in "acute idiopathic pericarditis" (7) whereas tuberculous infection of the pericardium, the chief differential diagnostic possibility in the present case, usually presents insidiously (8). "Acute idiopathic pericarditis" is two to ten times more frequent in males than females (4, 9) and has a peak age incidence in the fourth decade (9); however, it frequently is seen in older age groups (5, 10).

Chest pain is the most common presenting symptom in this disease (4, 6, 11), and is usually pleuropericardial in nature, being increased by motion, swallowing, deep inspiration and cough (9, 12). The pain is typically substernal or precordial in location and frequently radiates to the neck, shoulders and arms (9, 13). Over ninety-five per cent of patients with "acute idiopathic pericarditis" will have pain at some time during the course of their illness (12, 14). Our patient demonstrated the typical pain pattern of this disease. On the other hand, tuberculous pericarditis is often painless (4, 6, 8) and patients with uremic or rheumatic pericarditis rarely complain of pain (6, 7, 10).

Fever occurs in more than eighty per cent of cases of "acute idiopathic pericarditis." It may be as high as 105° and be associated with chills (9, 14). The fever may persist for a period of from two days to three months (14).

A pericardial friction rub is the most common finding on physical examination, being present in 50 to 75 per cent of cases (4, 9, 12), and is of varying intensity and duration (14). It should be noted that the disease can occur without a rub ever being audible. Pleural effusions are seen in approximately sixty per cent of patients and are usually left-sided or bilateral (5, 9, 12). Pulmonary infiltrations are somewhat less frequently found (5). Electrocardiographic (9, 10, 15, 16) and radiographic changes (17) of pericarditis may or may not be present (5, 6).

Leukocytosis (4, 9, 14) and an elevated erythrocyte sedimentation rate (9, 12) are common findings in this disease and were seen in this case. The serum glutamic oxaloacetic transaminase is usually not elevated, but increased levels may be seen if there is significant subpericardial necrosis (13, 18, 19).

While "acute idiopathic pericarditis" often has a short duration and a good prognosis, recurrences are common, occurring in approximately thirty per cent of cases (65). These may be multiple and produce prolonged disability as in our patient (27). In fact, the disease has been called "recurrent pericarditis" (4). It should also be emphasized that shock and cardiac tamponade are seen on occasion (7, 13, 20). These complications are rare but require immediate recognition and treatment. We believe that pericardiocentesis was a life-saving procedure in the present case. Frank effusions occur in about twenty per cent of patients with "acute idiopathic pericarditis" (21) and are usually sanguineous as in our patient (4, 6, 22, 23). There is some evidence that the disease can progress to chronic constrictive pericarditis, a point that will be discussed in greater detail later in this paper (5, 9). Several deaths have been reported in "acute idiopathic pericarditis," some of which occurred when patients had been inadvertently anticoagulated because of an erroneous diagnosis of acute myocardial infarction (7, 24, 25).

The induction of a pneumopericardium following pericardiocentesis is a valuable procedure and will usually demonstrate a smooth pericardium without nodularity in "acute idiopathic pericarditis" on post-tap films. These were the findings in our patient (Fig. 2). In tuberculous or neoplastic pericarditis, on the other hand, a thickened, ragged pericardium is seen (17).

"Acute idiopathic pericarditis" is undoubtedly of varied etiology. Several authors attribute it to hypersensitivity (26) and the syndrome has been reported to have followed injections of diphtheria and tetanus antitoxin (27). The most common cause is probably viral, and there are well-documented cases reported in association with Cocksackie viruses (28-30) and the viruses of influenza (31), mumps (32), primary atypical pneumonia (33) and infectious mononucleosis (34).

In view of the finding of granulomatous lesions in the pericardium, and the prolonged nature of this patient's illness, tuberculous pericarditis was seriously considered in the present case. Harvey and Whitehill (35) found that tuberculous pericarditis usually has a slow and insidious onset with malaise, weakness and anorexia as prominent complaints. While 25 per cent had dull vague chest pain, excruciating pain of acute onset, as seen in our patient, was

quite rare. The most common symptom was dyspnea, followed closely in frequency by complaints of peripheral edema and ascites. Only 25 per cent of patients were febrile. A pericardial friction rub was heard in only one-third of cases, while distended cervical veins, Ewart's sign, hepatomegaly, ascites and edema were found in over fifty per cent. The pericardial fluid was bloody in 14 and yellowish-green in 5 patients; and, in 4 of 5 cases, tubercle bacilli were cultured from the fluid during life. The authors pointed out that patients with tuberculous pericarditis either progressed to frank congestive failure or eventually had evidence of clinically apparent tuberculosis in other organs. Microscopic examination of the pericardium usually reveals chronic nonspecific granulation tissue.

Keefer (8) pointed out that coexistent tuberculosis of the lung or pleura was the exception rather than the rule in tuberculous pericarditis. Indeed, "primary tuberculosis of the pericardium," an entity in which no other clinically evident focus of tuberculosis is present, is frequently seen. Keefer also stressed the fact that the likelihood of finding tubercle bacilli was far greater in the presence of hemorrhagic fluid. Many of his patients were wasted, chronically ill and in cardiac failure. Stepman and Owyang (36) also commented on the difficulty of culturing tubercle bacilli from serous pericardial fluid, and pointed out that pneumopericardium, artificially induced after pericardiocentesis, invariably revealed a thickened pericardial lining in tuberculous pericarditis.

That this disease can be recurrent was shown by Janovsky *et al.* (37) who reported a patient who suffered recurrent attacks of chest pain simulating "acute idiopathic pericarditis." The diagnosis of tuberculous pericarditis was made after pericardial biopsy. Although histologically no tubercles were seen, culture of the tissue was positive.

Prior to the advent of antituberculous chemotherapy, almost all patients with tuberculous pericarditis died of their disease. Goyette, Overholt and Rappaport (38) treated 27 patients with drugs, bed rest and aspiration of fluid for relief of tamponade. This therapy was successful in 78 per cent of the cases with a rapid subsidence of symptomatology.

The diagnosis of tuberculous pericarditis in our patient is unlikely because of the sudden onset of the disease, the history of an upper respiratory infection preceding the appearance of chest pain by one week, and the fact that the patient never appeared chronically ill. The absence of thickening and nodularity of the pericardium after artificial pneumopericardium, the failure to culture tubercle bacilli from the pericardial fluid, the excellent clinical response to steroids without concomitant antituberculous chemotherapy (whereas in tuberculous pericarditis one would expect an exacerbation of the disease with such treatment), the repeated recurrences of the illness on steroid withdrawal despite continuing isoniazid therapy and the failure to find tuberculosis elsewhere represent other strong arguments against the diagnosis of tuberculous pericarditis. Unfortunately, cultures of the pericardial tissue were misplaced, but, in the present case, the weight of evidence is against a tuberculous etiology.

The pathologic findings in the pericardium made us also consider sarcoidosis

as a possible diagnosis. Sarcoid involvement of the pericardium is apparently quite rare and is not mentioned by Longcope and Freiman (39) in their review of sarcoidosis. In 1914, Schaumann (40) described a case with sarcoid granulomata in the pericardium, but since then only isolated reports (41-43) have mentioned the presence of such lesions at postmortem. As far as we could discover, there is not a single reported instance in which sarcoid pericarditis was evident clinically. In our patient, the lack of peripheral adenopathy and absence of visceral involvement, the failure to demonstrate granulomata on liver biopsy, and the negative Kveim test which, in this institution, is almost always positive in sarcoidosis make this diagnosis highly unlikely.

Granulomatous pericarditis may be associated with various fungal infections. Acute pericarditis has been described with histoplasmosis (44), actinomycosis, blastomycosis and streptothrix infections (6, 45), but is a rare manifestation of mycotic disease. That a fungus did not cause our patient's illness is evidenced by the negative cultures of the pericardial fluid, the negative skin tests, the lack of mycotic involvement of other organs and the dramatic response to adrenocortical steroids.

Other infectious agents, such as the various pyogenic bacteria, are capable of causing acute pericarditis and the syndrome may be seen in association with tularemia (46), echinococcosis (6), amebiasis (45), lymphogranuloma venereum (14) and toxoplasmosis (47). It is obvious that none of these diseases caused our patient's illness.

Diseases of connective tissue can cause the syndrome of acute pericarditis. Handfort and Woodbury (48) described a case of rheumatoid arthritis associated with a fatal pericarditis which followed a respiratory infection. Their patient had a hemorrhagic effusion and at autopsy had granulomatous lesions in the pericardium. These authors reviewed the literature and discovered several other cases of pericarditis secondary to rheumatoid arthritis. Our patient had no evidence of joint disease.

McCuiston and Moser (7) have reviewed the pericarditis occurring in disseminated lupus erythematosus and have attempted to differentiate it from "acute idiopathic pericarditis." These authors found that while lupus pericarditis is frequently painless, 28.6 per cent of their patients had an illness indistinguishable from "acute idiopathic pericarditis." This group did not have other manifestations of disseminated lupus for periods of from eighteen months to twenty-two years following their attack of acute pericarditis. They point out, as do other observers (49), that the L.E. phenomenon may be induced by pericardial fluid. Our patient had several negative L.E. tests including one performed on fluid obtained by pericardiocentesis. McCuiston and Moser consider an elevated white blood count and a history of a preceding respiratory infection, as found in our case, to be arguments against the diagnosis of lupus in a patient with acute pericarditis. These considerations and the granulomata found in our patient's pericardium make the diagnosis of lupus erythematosus most unlikely.

"Acute idiopathic pericarditis," the postmyocardial infarction syndrome

described by Dressler (50) and the postcardiotomy syndrome (26) have identical symptomatology. Dressler's syndrome usually responds dramatically to steroids, as did the present case, and may be present after a "silent" myocardial infarction. The lack of electrocardiographic changes of an infarction, the history of a preceding respiratory infection and the normal serum glutamic oxaloacetic transaminase level practically eliminate the postmyocardial infarction syndrome from consideration here.

Other causes of acute pericarditis such as trauma, neoplasm, uremia and acute rheumatic fever obviously do not apply to the present case.

We realize that "acute idiopathic pericarditis" is a diagnosis of exclusion (5); and, the finding of granulomata led us to search vigorously for a specific etiology. In the preceding discussion, we have pointed out that the lack of evidence for a specific cause, the history of a preceding respiratory infection and the dramatic response to steroids indicate that our patient's illness must be categorized as "acute idiopathic pericarditis." Further evidence supporting this thesis is the recurrent nature of her illness, on steroid reduction and the fact that there were three recurrences while she was being treated with isoniazid.

A search through the literature reveals only one previously described instance of granulomatous pericardial lesions in a patient whose clinical course was that of "acute idiopathic pericarditis." Movitt *et al.* (3) described two cases of acute pericarditis associated with Coxsackie virus infection. Pericardial biopsy in one of these cases showed "small granuloma-like foci and chronic inflammatory reaction." These authors did not elaborate further on the pathologic findings and the relationship to our case is hard to determine.

Gould, in his textbook on the pathology of the heart (51), describes the pathology of "acute idiopathic pericarditis" as "a serofibrinous reaction progressing to nodular and villous formation with pus in some cases." Histologically, the pericardium is at first covered with fibrin with many enmeshed polymorphonuclear cells and a few lymphocytes. Gradually granulation tissue was formed. He does not mention the presence of granulomatous lesions.

Proudfit and Effler (52) describe only nonspecific inflammation in their cases of "acute idiopathic pericarditis." Williams *et al.* (20) found "acute and chronic fibrinopericarditis and chronic inflammation" in four cases of "acute idiopathic pericarditis." Jaffe and Kallman reported a case of chronic pericarditis of unknown etiology associated with massive effusion treated with pericardiectomy (53). Histologic sections of the pericardium demonstrated "generalized thickening with fibrous tissue, nonspecific round cell infiltrates; no granulomata or intrinsic vessel changes were seen." Zinsser *et al.* (54-56), performed pericardiectomy on eight patients with recurrent benign pericarditis. In none were granulomatous lesions found. Several other authors (10, 11, 15, 22, 24, 25, 64) have described the microscopic appearance of the pericardium in this disease as that of a nonspecific inflammatory reaction.

We therefore believe that our patient is the second case to be reported in the literature of "acute idiopathic pericarditis" with granulomatous lesions of the pericardium.

An open pericardial biopsy was done in this case because of the prolonged course and lack of definitive diagnosis. Effler and Proudfit (27, 52) pointed out that traditionally pericarditis of undetermined etiology is considered tuberculous. However, a diagnosis of tuberculous pericarditis is often difficult to prove because specimens of pericardial fluid when smeared, cultured and inoculated into guinea pigs may be negative. They therefore performed open pericardial biopsy in a series of twenty-two patients for diagnostic reasons, and to create a pleuropericardial hiatus for the drainage of pericardial fluid into the pleural cavity. Two of these patients had positive cultures of this tissue despite a microscopic appearance of nonspecific inflammatory reaction. Williams and Soutter treated pericardial tamponade in "acute idiopathic pericarditis" in a similar fashion with good results (20).

Because of our patient's prolonged and disabling illness, consideration was given, on several occasions, to the performance of a pericardiectomy. Shumaker and Harris (58), Jaffe and Kallman (53) and Crastnopol *et al.* (59), all have reported the successful treatment of disabling recurrent massive pericardial effusion in "acute idiopathic pericarditis" by pericardiectomy. Zinsser and his co-workers (54-56) have extended this concept and now advocate pericardiectomy as the treatment of choice in recurrent disabling cases of this disease without effusion. They presented a series of eight patients all of whom had failed to respond to antibiotics and antituberculous chemotherapy and two of whom had no response to steroids. These patients had prolonged recurrent pericarditis. Pericardiectomy was performed under coverage with antituberculous chemotherapy with complete termination of illness in all cases. Zinsser stresses that most cases of "acute idiopathic pericarditis" are indeed benign and of short duration; but, he feels that those which are prolonged and recurrent should be treated with pericardiectomy. He prefers this procedure to the prolonged use of steroids because of the dangers inherent in the use of these drugs. In our patient, as was stated, consideration was given to pericardiectomy, but the subsidence of the illness on aspirin and the lack of further recurrences have precluded this form of therapy.

The response to steroids in the present case is of great interest. These drugs have been found to be useful not only in "acute idiopathic pericarditis" (65), but also in the postcardiotomy syndrome (26) and in Dressler's syndrome (60). However, while these diseases often respond to steroid therapy, several disquieting features attend their use. Kilbourne showed that the administration of steroids to animals inoculated with Coxsackie viruses produced extensive myocardial damage and spread of the virus (61). Since Coxsackie viruses have been shown to cause "acute idiopathic pericarditis" (28-30, 62), it is conceivable that steroids might aggravate and prolong the illness in such instances. Dressler reported a case of the postmyocardial infarction syndrome treated with steroids for two years with exacerbations occurring on their withdrawal (60). He emphasized that steroids should not be used in all cases of this syndrome but only in those patients who are severely ill. With respect to our patient, it was our clinical impression that her illness may have been prolonged by steroids. We therefore decided when steroid therapy was stopped for the last time, not to

reinstitute it as soon as pain and fever recurred but to reserve it for use only if the patient became critically ill. The patient did well with aspirin and has continued in good health since, without any medication. We therefore feel that steroids should be used in "acute idiopathic pericarditis" only in those patients who appear to be critically ill.

Chronic constrictive pericarditis, as a sequel to "acute idiopathic pericarditis," is apparently a distinct possibility. Paul, Castleman and White, in describing 53 cases of constrictive pericarditis, pointed out that in the majority of their patients no specific etiology could be found (63). In three of these patients, there was a previous history of acute pericarditis with development of constrictive pericarditis soon thereafter. In three other cases, there was a past history of an episode suggestive of acute pericarditis. Rabiner *et al.* (64), describe a forty year old man with "acute idiopathic pericarditis" with effusion, who underwent pericardiectomy two and a half months after the onset of his illness. At operation, the heart was found to be compressed by a thickened white visceral pericardium, and the ventricular excursions to be diminished. There was marked clinical improvement postoperatively. Two of Zinsser's eight patients with recurrent "acute idiopathic pericarditis" had constriction by the time they underwent pericardiectomy (55). To date, this problem has not appeared in the present case.

SUMMARY

This report deals with a patient with "acute idiopathic pericarditis" who presented with cardiac tamponade, was treated with steroids and had a prolonged course with numerous exacerbation of her illness. Pathologic examination of the pericardium revealed granulomata. Numerous studies were performed and failed to demonstrate a specific etiology. We believe that this is the second reported case of "acute idiopathic pericarditis" with such lesions. The differential diagnosis of acute pericarditis has been discussed and the pathology of "acute idiopathic pericarditis" has been reviewed. Several interesting facets of this disease were considered.

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WHAT CAN WE LEARN FROM EXISTENTIAL PSYCHOTHERAPISTS?

WILFRED C. HULSE, M.D.* ABRAHAM N. FRANZBLAU, M.D.,
AND HANS J. KLEINSCHMIDT, M.D.

New York, N. Y.

Dr. Wilfred C. Hulse (1): Verbal and written publications in the field of existential psychotherapy which intend to explain basic concepts and methodology of a new approach, have frequently not clarified but caused confusion and misunderstanding among us. This paper attempts to create better understanding in this area among our staff members who are in the majority, psychiatrists, *i.e.*, physicians who practice psychoanalysis and psychoanalytic psychotherapy in connection with general psychiatry.

I have avoided the use of the word existential analysis. It is used much—however, it seems a misleading term. The European term, generally accepted in French, German and English is "Daseinsanalysis"; L. Binswanger calls his last paper "Daseinsanalysis and Psychotherapy" (2). Rollo May gave his recent presentation the title "Existential Bases of Psychotherapy" (3). L. Binswanger says in the above-mentioned article that psychoanalysis and Daseinsanalysis are "both for their time entirely new *Erfahrungsweisen*" but that "the two *Erfahrungsweisen* are as different from each other as day and night," because the psychoanalytic one is interpolating, constructive and discursive, while the experience of existential analysis is a phenomenological "*Wesenserfahrung*" based on phenomenological "*Erfahrungsweise*." An "*Erfahrungsweise*" is a way of experience or experiencing. Freud, in a similar situation answered Binswanger when he used such words in his letters, that he was once more in the "claws of the philosophical devil." Binswanger explains the word "phenomenological" by saying that this approach tries to understand the "*Sache*" (*i.e.*, the thing one is interested in) "out of itself, *i.e.*, without alien theoretical constructions." Everything then—according to L. Binswanger, becomes a *Geschehen*, *i.e.*, a happening, in which "*es dem Dasein in seinem Sein wesentlich um sich selbst geht*." I have read this to you to listen to the frequently used alliterations (Dasein,—Sein); in the same way, Rollo May uses such alliterations when talking of psychotherapy, shuffling words like "aware," "beware" and "weary." The alliteration may be more important than the content which—in Binswanger's statement, actually says only that being is primarily concerned with itself and with self experience.

I do not intend to go on with this kind of explanation of philosophical terms because I want to present some aspects of psychotherapeutic methodology, namely; "What does an existential therapist do during a therapeutic session, what does he expect from his procedure and how does it work?" I have searched for answers to this question through reading, listening to papers, talking to and

From the Department of Psychiatry, The Mount Sinai Hospital, New York, N. Y. Read at the Monthly Psychiatric Staff Conference, January 3rd, 1961.

* Dr. Hulse has recently passed away.

having been acquainted with American and European existential therapists over many years—and more than anything else, from two rather unique personal experiences with Protestant theology; one in my adolescence during the First World War and the other during the Second World War in Central Europe as a neuropsychiatrist with the U. S. Army.

THE METHOD IN ACTION

I am going back to L. Binswanger because in his memories on Freud (4), he mentions repeatedly two things: his very early interest in Husserl's *Phenomenology* and Freud's repeated criticism of Binswanger's otherwise highly praised early case histories, Irma and the "Absatz" (heel) analysis; Freud objected that Binswanger draws conclusions from later life without adequate analysis of the early infantile and Oedipal periods. Here I think are the actual roots of the therapeutic approach—different of course from the philosophical one which I from now on want to reduce deliberately and consciously to a minimum.

Three important methodological aspects have to be understood, and they are indeed, to quote L. Binswanger again, different from psychoanalysis as "night from day."

1. A case history is carefully avoided and considered disturbing and prejudicing the physician. The "existential moment" is essential because there is a "Geschehen, in dem es dem Dasein in seinem Sein Wesenhaft um sich selbst geht." (A happening in which the existence is deeply involved with its own being.) Therefore past and future are kept out.

2. There is no diagnosis because this would involve "sachfremde, theoretische Konstruktion," i.e., "theoretical construction alien to it."

3. The real important and supposedly curative process is nonverbal and therefore not accessible to any of the clinical or scientific probings which we consider essential in our most important device of learning and teaching psychoanalysis and psychotherapy, namely supervision. The verbal evaluation is mostly limited to an exchange of opinion between patient and therapist about the question whether this "was a good session." No words might have been said by either. "This way we get a very effective session," I have been assured. The primary goal seems to be an immediate change in the patient's feelings.

It is obvious then that I can not give you, as I would like to do, the content of a session. However, I will repeat to you the essential aspects which, according to Rollo May (5), are taken up in the course of a therapeutic development in a case:

- 1) First, neurosis is seen as a method which the individual uses to preserve his existence and as the patient's significant way of shrinking the range of his world so that he can be adequate to the remainder.

- 2) The human being experiences his existence not automatically as given (as is the case with animals and the rest of nature) but rather as depending on his own self-affirmation. This is the "courage to be" as my old friend Paul Tillich calls it (6). Rollo May thinks that classical psychoanalysis underestimates this "because of its reaction against Victorian voluntarism and its discovery of unconscious determinants."

3) "Every existence has the need to go out from its own centeredness to participate in other organisms."

4) Every existence is characterized by awareness which is a reaction chiefly related to the sensing of threatening dangers ("awareness, weary, beware"—Rollo May).

5) A distinctive form of awareness which is termed self-consciousness, *i.e.*, the capacity to be aware of oneself as living and existing in the world. The function of therapy is not only to increase this awareness, but even more significantly, to transmute awareness into consciousness.

6) Anxiety is the state of the existence as it stands and struggles against that which would destroy its being. The existential approach emphasizes the potentially constructive function of anxiety and guilt and seeks to help the person use them for increased consciousness, sensitivity and creativity.

All this appears to be a lot of old wine, somewhat watered down and served in new vessels; However, the preference for the essentially nonverbal approach in dealing with the patient is difficult to understand; it is suggested that if "self-realization" and "self-expression" are the primary goals, the nonverbal, nonrationally controlled process might be commensurate to this esoteric task of a completely subjective goal.

DISCUSSION

If we want to understand in our own terms this procedure, we will have to break the rule of Daseinsanalysis—not to make an anamnesis and not to make a diagnosis. I will try to use our old, effective, and proved methods for exploration.

The nonverbal, essentially anti-intellectual, mystical and inner-experiential approach, is not new. It precedes Kierkegaard, Husserl, Heidegger, Sartre, Binswanger, Tillich, Martin Buber, Ellenberger, May and others by many, many centuries.

The roots are, as Freud has shown us, often more accessible when we turn to literature than when we try to walk along the routes of science (7). The recent successes on the New York stage of Archibald MacLeish's "J.B." and Becket's "Waiting for Godot," guide us back to the Old Testament, in the books of Job and Ecclesiastes, and also to the much younger, new testamentarian "Book of Revelations" which reports the inner experiences of St. John of Padmos.

While I was preparing this paper, I happened to see a case in point, a very bright 19 year old female patient with retrolental fibroplasia and blindness from the first weeks of life. She gives a lifelong story of isolation, rejection, insecurity and difficulties to attach libido to well-selected objects, a very difficult task for a person who does not know what vision is. In her despair, she has developed a very existential, very depressed attachment to a religious sect devoted to the Book of Revelations and its essentially despairing and fatalistic story that the day of reckoning is coming within a few months and that nothing but prayer counts. This seems a valid defense for an untreated chronic severe depressive character disorder with a severe physical handicap. We are dealing here with a very pertinent individual reaction; similarly, existentialism is a group reaction

to the desperate massive depression of our times. In all times, theologians have drawn from the mystical teachings of Job, Ecclesiastes and St. John to console those in despair. It is not a coincidence that some of the leading figures of the contemporary existentialist psychotherapy movement and of Daseinsanalysis come from interestingly similar backgrounds. Let us remember that Switzerland is the breeding ground of mystical sects and schisms and that Hermann Rohrschach, whom most of us know only from his test, had devoted most of his short life as a psychiatrist to do research and to publish on the psychiatric aspects of these Swiss mystics. The Swiss are very inclined toward this mystic approach, the simple mountaineers as well as the old patrician, highly intellectual and cultured families like the Binswangers and Medardus Boss.

Paul Tillich and Martin Buber are theologians of the highest caliber who have always been swaying from fundamentalist orthodoxy and chassidism to liberalism, to psychoanalysis and back into "Daseinsanalysis" (8). Rollo May comes from theology and Ellenberger has told of his childhood days in South Africa as the son of fundamentalist Swiss missionaries. When war came Dr. E. Minkowski in Paris stayed in the underground and saved the lives of hundreds of Jewish children. When I got to Paris shortly after the Nazis had left, he was in despair. The great task was done but had left him depressed and empty. After this he became a leading existential psychiatrist (9).

The clearest case in this respect is of the Vienna existential analyst Victor Frankl who now calls his slightly different brand of approach Logotherapy (10). Shortly after his religious conversion in a concentration camp and before he joined the general trend using the word "analysis" for this type of psychological ministry, he wrote in 1947 a little book entitled "Aerztliche Seelsorge"—and it is this essentially religious book in which the core of the present movement is clearly presented (11). "Aerztliche Seelsorge" means "Medical Care for the Soul" and it is this old and well-integrated function of the German and Swiss Reformation of Luther, Zwingli, Calvin and their ministers which we find again in the present-day movement under the more fashionable name of existential or Daseinsanalysis. It is communion of souls that the Protestant minister of the German cultural area wants to bring to the poor, the sick and the suffering; he joins them by being with them, sitting with them, letting them know that they, the desperate, the abandoned, the mourning and the dying are not alone. Words are not essential for this ministry; scientific procedure, diagnosis, anamnesis and katamnesis are not essential, but being and feeling with them is essential.

I think that all of us can understand with sympathy such a movement that brings support and consolation to those who today feel abandoned by the not uncommon type of minister who does not practice "Seelsorge," but is often preoccupied with fund raising, the arrangement of bingo games, and young people's picnics. "Seelsorge" is also a necessary function of the family physician who does not rely on his laboratory alone but uses softly and understandingly the consultation room and the bedside as the place for dealing with human beings in despair, fear and anxiety, and who does not "analyze" or practise organized psychotherapy but who, when there is need, supports, consoles and stands by closely.

I have mentioned before that I have had twice in my life the chance to live intimately with the practise of Seelsorge for the abandoned and downtrodden, and I can appreciate its value. Once, through a peculiar twist of circumstances I lived with the family of a German Protestant minister during the four years of the First World War and became intimately acquainted with him and his high-minded minister friends who had to struggle against the essentially un-Christian task which the first World War in Germany imposed on the ministry. The second time, during the Second World War in Europe through another twist of circumstances, as a U.S. Army Captain and chief of neuropsychiatry, I was the only German speaking American officer in charge of the rehabilitation and spiritual care of 200 German Protestant POW's who were in deep despair. My only assistance was from a Protestant Chaplain, a high-minded non-believing Southern Baptist with the finest spirit of responsibility, but without any knowledge of German religious thinking or language. Again I had to learn and to appreciate what "care of the soul" means for the physician.

However, this is neither the practice of psychoanalysis nor of psychotherapy. It is not geared toward, nor is it effective in dealing with psychopathology; it is neither a scientific nor a curative method. It is sometimes a very useful, teachable and learnable auxiliary service in medicine and we can accept and practice it, without accepting the strange need of some people to use the words: psychoanalysis, analysis or psychotherapy for this essentially unscientific but humane, charitable and more or less religious approach.

I would like in conclusion, to speculate briefly on the psychoanalytic meaning of this type of approach. Freud was never as unkind with Binswanger as he had to be with Carl Jung. His strongest disapproval of Binswanger was contained in the good-natured advice: "let's be friends and stick to psychoanalysis; leave me alone with religion because you should know that this is not for me!" However, even in those parts of the correspondence which Binswanger has published, one can find Freud raising questions about the inadequate analysis of early childhood sexuality in Binswanger's cases several times. As in Jung, one can find in the Daseinsanalyst the same reluctance, (possibly due to remaining religious taboos), to analyze the early sexual, especially homosexual conflicts and fantasies of their patients. We can find the same trend in the present approach of existential analysis and psychotherapy. While the attempt to permit the distressed patient identification with a parent is helpful, this parent remains a threat and must enforce repression through the nonverbalized fantasies which are never interpreted and are touched upon only in vague, mystical terms. The greatest danger is possibly this stimulation of both heterosexual and especially homosexual fantasies, which then become increasingly reveries in the sense of the Revelation of St. John. It seems that many ambulatory schizophrenics are greatly attracted by this kind of preconscious soothing, vague and mystical approach. It would be interesting to have a scientific psychoanalytic evaluation of the results of this "Seelsorge" approach in definitely diagnosed psychiatric patients, not only in terms of their subjective feelings, but in terms of the state of their psychopathology and the chances for recovery under this type of treatment.

SUMMARY

This paper attempts to explain function, methodology and goals of the different existential therapeutic methods (*i.e.* existential analysis, Daseinsanalysis, Lebens Analysis, Logotherapy, and existential psychotherapy), in terms of psychoanalytic psychology in order to stimulate better understanding among psychoanalysts and psychoanalytic psychotherapists. The paper deals primarily with psychotherapeutic dynamics and only to the barest extent with the philosophical roots of existential treatment methods, leaving the aspects of religion and philosophy to the discussants.

The paper concludes that the existential treatment approaches are valid auxiliary methods to help people in mourning, discouragement and despair and that they come closest to the ministry, especially as practiced by Protestant ministers in the Swiss-German cultural area under the designation of "Seelsorge" ("Care for the Soul"). The conclusions also suggest that these methods are basically unscientific as they refuse to set up proper methods of diagnosis, supervision and control. They are, as L. Binswanger has said, different from psychoanalysis "as day from night". It is therefore misleading and possibly dangerous to designate these methods as psychoanalysis, analysis or scientifically applied psychotherapy. Caution is advised in their use in cases of serious psychopathology. However, they can serve well as auxiliary methods in handling human beings in need of support.

Dr. Abraham N. Franzblau: Before discussing existential psychotherapists, we ought to take a look at existentialism, *per se*. Freud said, in "The Future of an Illusion," that man's impulse to create for himself religious beliefs stems from three main facts: 1. Nature is cruel and capricious, showing man no favor; 2. As far as man can possibly know, death is the inescapable end of life; and 3. Man cannot face the hazards of living, all by himself, hence must yield pleasures in return for the help of his fellow men. All religious beliefs are intended to counteract, soften or sanction these facts.

Existentialism appears to place Eros and Thanatos in a reverse order. It says: 1. Man is isolated in history and society—has no sense of past or future; 2. He must develop through his own efforts—he "is what he is doing" (a striking contrast with Buddhism). There are Aristotelian notions in it (potentiality and actuality; essence and existence), and Kantian notions (man organizes his chaotic world within his mind under space and time contexts); 3. Everything is subjective—man is *confronted*, having no past and future, he has no promise of redemption nor purpose in existence, hence must go it alone and do it himself; 4. The only sure fact is his own death (not life), hence he lives on a precipice all the time. Religion reacts by positing a Hereafter, psychoanalytic theory by countering Thanatos with Eros in mature acceptance, but existentialism with pessimism and desperation alone.

Existentialism appears to be philosophically unsound, having no system, no architecture, no theory of knowledge, metaphysics, ethics, or epistemology. It is seemingly esoteric, but the more popular it becomes the more exoteric it becomes. It is given to using obscure and neologistic terminology, for example:

Heidegger: "a time-producing form of temporality"; "... letting-be"; "... Time is the existential horizon upon which man's being-in-the-world discloses itself"; "... one tends to appreciate nonduality as the realm of True-Suchness"; *Buber*: "... the essentially dialogic nature of man"; "... transcendence of the temporospatial coordinates of existence"; "release from his epistemic isolation"; "he has turned his exposedness into holy insecurity"; *Hora*: "Being with a person in the spirit of *letting-be* makes it possible to comprehend this person in a transjective, that is, experiential way"; "The striving, intentional man lives in the sphere of discursive-inductive modality of knowledge... He is accessible to the phenomenological-empirical modality of knowledge..."; *Krishnamurti*: "... *"non-evaluation, choiceless awareness of what is."* (12).

I agree with Dr. Hulse's fine presentation of existential psychotherapy, that it is "nonverbal, essentially anti-intellectual, mystical, inner experiential," and that it represents "cure of souls," rather than therapy in a psychiatric sense. I would add that it is not "cure of souls" in the sense in which the Christian ministry has practiced it over the centuries, and its therapeutic results are most comparable to Christian Science or Lourdes. Dr. Hulse points to its essential mood of despair, even desperation. It is interesting to note how many of its outstanding leaders and thinkers had warped boyhoods with domineering, tyrannical fathers, and were unable to love a woman. Sören Kirkegaard, who had such a father was engaged for years to Regina Olsen, a lovely girl, but he broke the engagement, unable to face marriage. To be what he calls a "single one," a solitary man whose contact with the world is broken is, to him, the only way to salvation. He says: "In order to come to love, I had to remove the object." Martin Buber, commented on this: "God wants us to come to Him by means of the Reginas he has created, and not by renunciation of them." Heidegger says that only through death can we achieve life—"... *dasein* is always running forward in thought toward Death."

The attitude of existential psychotherapy toward psychoanalysis may be summed up, perhaps, by quoting Medard Boss to the effect that everything that Freud wrote about technique is right, but everything he wrote about theory is wrong (13). Yet even the technique is rejected by many. Hora stated, "Free association reveals itself to us as a misnomer containing a double contradiction. First, it is not free because it is *intended* to be free; second, it is not free because it is to serve a *purpose*." "... The existential psychotherapist does not 'do' psychotherapy, he lives it. He meets his patient in the openness of an interhuman existential encounter." (Isn't this like 'love' in the Christian ministry?) "The existential psychotherapeutic process... brings man into harmony with the essence and destiny of All Things... the so-called psychic mechanisms of transference, countertransference, projection, introjection, identification, resistance and empathy, lose much of their significance and reality."

The patient's relationship with the existential therapist is defined variously, but always in highly abstract, mystical and subjective terms. (*i.e.* *Buber*—"intersubjectivity"; *Marcel*—"mutual spiritual inclusion"; "being-in-the-world as transcendence"; *Roger*—"Total presence, *i.e.*, total organismic sensitivity to

the other person"; *Sozan*—"In the higher realm of True Suchness there is neither 'self' nor 'other' . . . We can only say 'not two'"; *Krishnamurti*—"understanding is 'action which is non-action'" . . . "the subject-object dichotomy is transcended" . . . ; *Hora*—"the alternative for all those attitudes" (i.e., the rejected psychoanalytic techniques) "... is *letting-be*, not to be mistaken for leaving alone".)

In existential psychotherapy there may be good counseling, sound common sense, friendship and helpfulness, and the givingness of love, all related to the kind of helpfulness to people which is the mark of the ministry of all faiths from time immemorial (like "cure of souls" in the Christian ministry, or the ministrations of the Chassidic Rebbe in Judaism). However, its matrix of mystic manipulation of words and meanings and its subjective interrelationship of patient and therapist in a mist of mutual emotionality leaves little room for it in the armamentarium of scientific psychotherapies.

Dr. Hans J. Kleinschmidt: It hardly seems appropriate to ridicule existentialist psychiatry or to label its terminology "schizophrenia." No matter how alien its language and concepts are to us—they deserve exploration and understanding. We might do well to remember first of all that existentialist concepts are rooted in phenomenological observations, in attempts to comprehend the way things are and how people feel rather than to analyse why people feel the way they do or why things are this way instead of any other. In this sense existentialist psychiatry is antianalytical and antidynamic.

Binswanger tried to fuse psychoanalysis and existentialism, pointing out that man's highest aspirations and attainments had to be more than sublimated instincts. He tried to separate the lofty ideals of the 'homo cultura' from the instinctual impulses of the 'homo natura.' As an experienced clinician he recognized the limitations of a purely phenomenologic description and therefore insisted on using psychodynamics in order to understand a patient's early life experiences and specific aspects of a case history. Others, analysts and clinicians, especially in Switzerland and Germany, have followed Binswanger's example of trying to reconcile both points of view, the psychoanalytic and the phenomenological. That these two are antithetical, is not accepted by the so-called existential analyst.

Dr. Hulse's remarks elucidating the link between existentialist psychiatry and theology were particularly interesting to me. One is reminded of Paul Tillich's emphasis on the 'Kairos,' the significance of the psychological moment of the encounter of two people. If we understand Binswanger correctly, then the phenomenology of this encounter constitutes the basis of existentialist psychiatric observation.

Where Sartre speaks of man's fear of just this encounter with another because it can only lead to conflict between two 'subjects,' each one diminishing the other to some extent by objectifying him—there Binswanger introduces the humanistic concept of approaching the other being with sympathy and understanding. According to Binswanger, the importance of the encounter lies pre-

cisely in reaching out toward the patient in terms in which he experiences the world, in order to arrive at a fruitful and authentic communication.

While existentialist psychiatry reveals close links to theology, its roots lie in philosophy. Karl Jaspers, a disciple of Husserl and Max Weber, has exerted a profound influence upon intellectual youth in Germany, Austria and Switzerland. A university instructor in psychiatry, he turned to philosophy after his personal disappointment in psychoanalysis. His *General Psychopathology* which first appeared in 1913, and which had seen five editions by 1948, became the most widely used textbook by students of psychiatry in Germany. In it he attacked Freud for not being concerned with the higher values of moral and spiritual nature; he warned of a psychology which bases all psychic phenomena on sexual drives; he spoke of Freud's concept of "sexuality in a wider sense" as the ultimate reduction of all emotional manifestations while Jaspers failed to explain the meaning of the concept of libido or Freud's contributions to ego psychology. But then, as Oskar Pfister pointed out in his paper 'Karl Jaspers as Adversary of Sigmund Freud,' Jaspers proudly ignored Freud's work after 1910 with the exception of an "occasional sampling" of psychoanalytic literature. In many of his later writings such as *The Spiritual Situation of our Time* which has seen five editions since its publication in 1930, *Reason and Unreason in our Time*, *Marr and Freud*, both published in 1950, he continued to attack Freud for his lack of spirituality and postulated that the individual in our era was threatened by three powerful and destructive forces: modern technology, the Marxist doctrine, and Freud's instinct theory. His warnings and dire forebodings always culminated in what he called a "comprehensive psychology" and vague philosophical generalities, in part taken from Heidegger.

It would appear that existentialist psychiatrists are trying to push the clock back, aided by theologians and philosophers who seem intent on reclaiming psychology and psychiatry for the faculty of philosophy. The motivations are many. One may be to bypass the cruel facts of man's common biology and his mortality, that which the existentialists like to call our "temporality." Another one seems to be the vexing issue of man's responsibility for his fate. It is easier to point an accusing finger at "the times" and society at large than to assume responsibility as an individual. Existentialism therefore is not only antianalytic and antigenetic, but also opposed to the concept of unconscious psychic determinism. According to existentialist authors, this concept interferes with man's free choice. We believe, instead, that man's freedom of choice is reinforced by making the unconscious workings of the psyche conscious.

The deep concern with man feeling at odds with society, a recurring theme in existentialist writings, is not new. Thomas Mann struggled with it in *Tonio Kroeger* and again in *Doctor Faustus*. So did Nietzsche and before him Goethe in *Die Leiden des jungen Werther* and so did Heine and other poets and writers in the Romantic Movement. But Thomas Mann was capable of a deeper understanding of the contribution psychoanalysis has made. He saw in Freud the pioneer of a future humanism.

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PAROXYSMAL PHENOMENA RESEMBLING SEIZURES, RELATED TO SPINAL CORD AND ROOT PATHOLOGY

MORTON NATHANSON, M.D.

New York, N. Y.

Included in the category of paroxysmal disorders of the nervous system are several conditions that are not clearly understood as to pathophysiology. Such episodic disorders as trigeminal neuralgia, facial spasms and lightning pains in tabes dorsalis have been considered empirically as "seizure" discharges and reports of control of these episodes with anticonvulsants have more recently appeared. Aside from the reports that dilantin sodium controls these attacks in some individuals, there has been little or no evidence that "removal" of the *pathology* or causative agent will also stop the episodes short of cutting the nerve root or perhaps destroying nervous tissue by direct or stereotaxic methods. During the past three years, two patients were studied whose initial complaints were frequent, brief episodes of pain and associated involuntary movements of one lower limb that in appearance suggested seizures originating in the opposite parasagittal region of the cerebrum. These attacks occurred spontaneously, lasting ten to twenty seconds, and ceased rather abruptly. Both patients were found to have gross "irritating" lesions (cord and root) that were surgically removed and followed by cessation of the attacks.

CASE REPORTS

Case #1. R.S. A seventy-five year old woman was referred for neurologic evaluation in November, 1957, and was admitted to The Mount Sinai Hospital the following day. She gave a four year history of frequent attacks of "burning and spasm" of the left lower limb. She stated that the attacks started suddenly without warning at any time of the day or night, occurring about eight to ten times a day. The burning pain began in the left buttock and groin and spread to involve the entire limb in a matter of seconds. It was accompanied by involuntary "stiffening and raising" of the left thigh and leg. The entire episode lasted "about fifteen to twenty-five seconds," ending as abruptly as it began. This was followed by "tiredness" of the entire left lower limb. In addition, she complained of occasional periods of numbness of the right lower limb, and at times urgency and frequency of urination. She denied associated loss of consciousness, mental confusion, involuntary movements of the other limbs, and symptoms referable to the cranial nerves. Three months prior to this examination "a cyst was removed from my left kidney but the attacks continue." The background history was otherwise noncontributory.

Examination revealed the patient to be mentally clear in all spheres. The cranial nerves were normal. During the initial and subsequent examinations a number of identical attacks were noted by different observers. While the patient

From the Department of Neurology, The Mount Sinai Hospital, New York, N. Y.

was seemingly relaxed and comfortable, she suddenly complained of severe burning pain in her left buttock and lower limb and simultaneously the entire left lower limb began to stiffen, the thigh slowly flexing on the hip as the leg partially extended. The toes were noted to dorsiflex. No clonic movements were observed. The patient remained conscious, and although she grimaced with pain, was able to answer simple questions and carry out simple commands. She could not, however, voluntarily alter the position or attitude of the left lower limb during the attack. Each attack lasted eighteen to twenty seconds. Following the abrupt cessation of the attack, there was weakness in dorsiflexion of the left foot and flexion of the knee that lasted approximately five minutes. Between attacks there was good power in all limbs. The knee and ankle jerks were hyperactive and the plantar responses were equivocal. Vibratory sense was absent from the midthoracic region down, including the sacral area. Other modalities of sensation were intact. Percussion of the spines and straight leg raising tests elicited no pain.

Although the episodes suggested right parasagittal discharges, the neurologic examination pointed to cord involvement. Complete blood count, urine, sedimentation rate, fasting blood sugar, urea nitrogen, alkaline phosphatase, serum calcium phosphorus, total protein and A/G ratio, and serology were normal. X-rays of the skull and chest were negative. X-rays of the cervical, dorsal and lumbosacral spines revealed moderate hypertrophic changes and mild osteoporosis. The pedicles and interpedicular distances were normal. Lumbar puncture revealed clear and colorless fluid and the total protein was 200 mg%. There was a complete manometric block. Pantopaque myelography showed a complete block at the middle of the body of the first dorsal vertebra. The electroencephalogram remained normal even during one of the episodes. Amytal test for underlying cerebral dysfunction was normal. A right carotid angiogram was refused; in fact, the patient refused operation for the spinal cord tumor at this time.

She was discharged on dilantin sodium and reported that the frequency of the attacks was definitely less. However, after four months the attacks again increased in frequency. Finally she consented to operation and was admitted for the second time on July 10, 1958. The episodes still had the identical characteristics as previously observed, and the neurologic status was changed only in that there was now moderate weakness of both lower limbs. She was operated upon on July 17, 1958, and a meningioma at the level of the first thoracic vertebra was removed.

Following operation, the attacks decreased in frequency from 8 to 10 times a day to 1 to 2 times a day, and by the fourth postoperative week, they ceased. She has not had any attacks since and has not been on anticonvulsants. Eighteen months after the operation she complained of pain over the operative site and right shoulder, but refused further investigation.

Case #2. J.R. A sixty-two year old man was admitted to The Mount Sinai Hospital on September 16, 1959, with a six week history of attacks of severe, knifelike pain in the low back, radiating down the posterior aspect of the right

thigh and leg, and accompanied by "twitching and jumping of my leg and foot." Each attack lasted a matter of seconds and occurred as frequently as twenty to thirty times a day. Between the attacks there were no complaints. Coughing, sneezing, or straining at stool failed to elicit the attacks. He claimed that at times "if I leaned on my right buttock or rested on my right side" the attacks were more prevalent. However, the episodes also occurred when he was at rest sitting or lying on his left side or flat in bed. They occurred, too, when he was standing or walking. He stated that the "twitching and jumping" started in his right toes and foot and then involved the leg. The "twitching and jumping" subsided moments after the pain stopped. He denied weakness or paresthesias of the limb following the attacks. In 1914 an operation for a slipped cartilage in his right knee was performed with no sequelae. The background history was otherwise noncontributory.

Examination between episodes revealed a normal mental and neurologic status. There was no weakness of the limbs. Percussion of the spines and straight leg raising tests elicited no pain. The deep tendon reflexes were present and equal. There were no pathologic reflexes. All modalities of sensation were intact.

Numerous episodes were observed by different examiners and were characterized by a sudden complaint of severe, sharp pain in the low back with radiation down the posterior aspect of the entire right lower limb. At this point he would say, "There it goes," and it was noted that the toes of the foot began to spread and jerk, followed by the foot and then the leg. The appearance was that of a clonic seizure which lasted ten to twelve seconds. Plantar flexion of the foot and flexion of the leg by the examiner failed to stop the attack. Following the episode, there was no change in plantar responses, deep tendon reflexes, motor power, or sensory perception. At times digital pressure exerted by the examiner over the sciatic notch or along the course of the sciatic nerve in the thigh elicited a full attack.

X-rays of the skull, spines, and chest, and intravenous pyelogram were normal. Complete blood count, urines, sedimentation rate, fasting blood sugar, urea nitrogen, serology and total protein and A/G ratio, acid and alkaline phosphatase, and urines for porphobilinogen were normal. Electroencephalogram was normal. Lumbar puncture revealed clear and colorless fluid, no cells, total protein 80 mg% and negative serology. Pantopaque myelography showed a significant defect at L4-5 interspace on the right. The remainder of the pantopaque column in the spinal canal up to the clivus was normal. Because of the normal neurologic status, laminectomy was deferred and the patient was discharged for further observation on dilantin sodium. At first he claimed that the episodes were less frequent, but soon stated that they were occurring more frequently than ever. However, he continued to work as an elevator operator.

He was readmitted on August 26, 1960. The observed episodes were identical to those of the previous admission. Prior to laminectomy, a left carotid angiogram and pneumoencephalogram were performed to rule out left parasagittal lesion and they were normal. Operation revealed an extruded disc compressing an abnormally large nerve root. Following operation he had several more epi-

sodes during the next five days. Since the sixth postoperative day to the present (eight months) he has not had a single attack. Except for an absent right ankle jerk, the neurologic status remains normal, and he has been engaged in full time employment.

DISCUSSION

The problem of spinal cord convulsions has been investigated in animals by Esplin and Laffan in 1957 (1) and Esplin in 1959 (2). They stressed the significance of spinal reflexes in determining a seizure pattern. Esplin in 1959 stimulated the spinal cord of cats after section below the medulla. He showed that continuous maximal stimulation of the cervical cord under these conditions resulted in a "sequence of hind limb movements identical with those seen in the maximal electroshock seizure and in the grand mal epileptic convulsion." He also demonstrated that the tonic motor response to low stimulus frequency outlasted the period of stimulation. In addition, common anticonvulsant drugs were found to be somewhat less effective in preventing cord seizures than seizures produced by cerebral stimulation.

The pattern of the tonic episodes involving the left lower limbs in Case #1, followed by a brief postictal weakness seems comparable clinically to Esplin's observations. Dilantin sodium, grains $1\frac{1}{2}$, three times a day, appeared to decrease the frequency of episodes for a time but later failed. Perhaps increased dosage would have been effective. However, following the removal of the meningioma (cord "stimulus") there were no further episodes.

As to root or cranial nerve "seizures," there has been an accumulating body of presumptive evidence that these structures may initiate their own epilepticlike episodes. Korey has shown that dilantin sodium produced depressed action potentials in the giant axon of the squid (3). More recently Morrell, Bradley and Ptashne showed that dilantin sodium increased the threshold to electric stimulation of mammalian peripheral nerves *in situ* (4). Iannone, Baker and Morrell have utilized the information from the previous studies and found that dilantin sodium was effective in selected cases of trigeminal neuralgia (5). Green has reported on the efficacy of dilantin sodium for lightning pains associated with tabes dorsalis (6).

In Case #2, the attacks of pain along the sciatic distribution associated with clonic movements of the toes, foot and leg were only partially controlled for a short period with dilantin sodium. Here too, perhaps dilantin sodium given in doses greater than grains $1\frac{1}{2}$, three times a day, would have controlled the attacks. However, the remarkable effect of removal of the herniated disc may indicate that as in Case #2 the stimulus was too great to be overcome by the average dosage of dilantin sodium.

SUMMARY

Two patients with episodes involving one lower limb having the appearance and many characteristics of seizures commonly attributable to a cerebral discharge, were relieved of these attacks after removal of the causative pathology,

a meningioma at the T-1 level and a herniated disc at L4-5 on the right. Both had trials with dilantin sodium eight months and eleven months respectively, without control of the seizures. These cases corroborate the increasing clinical and experimental observations that the spinal cord and nerve roots may initiate their own "seizure" discharge.

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STUDIES ON THE PROGRESSION FROM ACUTE HEPATIC INJURY TO FIBROSIS OF THE LIVER

A PROGRESS REPORT

HANS POPPER, M.D., TIBOR BARKA, M.D., STANLEY GOLDFARB, M.D., FERENC HUTTERER, M.D., FIORENZO PARONETTO, M.D., EMANUEL RUBIN, M.D., FENTON SCHAFFNER, M.D., EDWARD J. SINGER, Ph.D., AND FREDERICK G. ZAK, M.D.

New York, N. Y.

Our studies of acute hepatic injury as well as of the various processes leading to and associated with hepatic fibrosis and cirrhosis have recently been extended with the same techniques applied in the past (1). These included clinical pathological correlation, conventional microscopy supplemented by fine structural techniques, including electron microscopy, histochemistry and immunocytochemistry, as well as by biochemical procedures such as chemical pathology and cytochemistry. Some aspects have been studied in cooperation with other groups. Recently, in addition, autoradiography and immunologic techniques have been utilized and were responsible for emphasis on the character of the initial hepatic injury and on the immunologic alterations which are associated with the chronicity of hepatic lesions. The basis of this study was again human material obtained by biopsy and necropsy as well as tissue and fluid of rats in which a variety of pathologic changes had been produced by experimental procedures. In the course of the investigation the functional significance as well as the pathogenesis of the proliferation of bile ducts became a key problem relating to many of the studies to be reported. Moreover, the attempt to therapeutically influence chronicity in hepatic disease led to a more intense investigation of the effect of corticosteroids. This problem in turn has been associated with the question of the biochemistry of hepatic fibrosis (2).

INITIAL HEPATIC INJURY

Alterations in a variety of conditions which may or may not be followed by fibrosis and cirrhosis have been studied as the response of the liver to injury (3).

A. *Viral hepatitis*. Electron microscopically, the degree of damage throughout the liver and throughout the cells varied, with the most prominent feature being loss of granularity, vacuolization and fragmentation of the endoplasmic reticulum (4). In a few cases unusually large dense bodies lined the endoplasmic reticulum which seemed to represent abnormal ribosomes or Palade granules and resembled the bodies previously described as possible virus particles (Fellinger and Braunstein, Gueft). Swelling of mitochondria occurred only in severe and more protracted cases and in the most severely damaged liver cells. In instances of drug-induced hepatic damage resembling viral hepatitis (*e.g.* produced by

From the Department of Pathology, The Mount Sinai Hospital, New York, N. Y.

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monoamine oxidase inhibitors), similar alterations of the endoplasmic reticulum were noted but so far no abnormal ribosome-like bodies were observed (5). The hepatocytes varied throughout in ATPase and 5-nucleotidase activity. The biliary microvilli were altered in patients with clinically apparent cholestasis but were otherwise intact. They frequently showed decreased ATPase and 5-nucleotidase activity, indicating impaired biliary secretion. Lysosomes were increased and acid phosphatase granules were spread throughout the cell. The cell borders were not necessarily involved but alkaline phosphatase activity in the sinusoidal walls was greatly increased. The ductules appearing proliferated on conventional microscopy contained increased acid phosphatase and their luminal border reacted strongly for 5-nucleotidase. Electron microscopically they revealed lifting up of the basement membrane by edema. An extensive inflammatory reaction composed of a variety of cells (see mesenchymal reaction below) and excess fibers were noted around damaged liver cells and proliferated ductules.

B. *Subacute ethionine intoxication*. In rats exposed to an 0.5% ethionine containing diet for 5 to 7 weeks, the electron microscopic picture exhibited a similar lack of uniformity as apparent under the light microscope. Even within the same cell different degrees of injury were noted in different areas. However, entirely normal areas were not seen. All mitochondria showed swelling, some to larger than four times normal size with loss of cristae and decreased density of matrix. The endoplasmic reticulum varied from severe vacuolization with loss of the accompanying ribosomes to complete disruption throughout the entire cells. Occasional fat droplets up to 2 to 5 microns in diameter were found. Lysosomes, bile canalicular microvilli and the other parts of the cell border were not altered. There were abundant epithelial cells of bile ductules with more endoplasmic reticulum than normally seen in such cells. Moreover, fat pigment or iron granules were found in their cytoplasm, depending upon the age of the lesion. Their biliary border was rich in 5-nucleotidase and in nonspecific alkaline phosphatase. These cells took up tritiated thymidine indicating rapid proliferation. Around the ductules increase of mesenchymal cells was noted, many of them engaged in phagocytosis, as well as excess of fibers. It thus appears that the primary insult involves the endoplasmic reticulum and or mitochondria of the hepatocytes associated with rapid formation of ductular cells which contained more cytoplasmic organelles than normally found. The life span of these cells in preliminary experiments appeared reduced.

C. *Cholestasis*. In human extrahepatic and intrahepatic cholestasis, bile appeared as multiple ringlike small structures in empty cytoplasmic spaces, dense granular material, or as very large, dense, intracellular lakes. More lysosomes than normal were found and they were less concentrated around bile canaliculi. Increased amounts of acid phosphatase granules were noted which also were spread throughout the cells. ATPase was decreased depending on the degree of canalicular dilation. Alkaline phosphatase was greatly increased both in the canalicular border and along the sinusoids. The previously described alterations of the microvilli were confirmed. The endoplasmic reticulum was vacuolated and

fragmented while mitochondria showed curved distortion of cristae. The primary insult thus appears to involve bile canaliculi and subsequently endoplasmic reticulum, lysosomes and mitochondria. In four cases of primary biliary atresia in infants, the same features were noted. In six cases of primary biliary cirrhosis, all of them with repeated biopsies, the electron microscopic and histochemical changes, despite clinically severe cholestasis, showed no characteristic abnormalities.

D. Giant cell hepatitis of infancy. Of this variety of hepatitis of infancy with cholestasis and with problematic relation to viral hepatitis, five cases were studied, all with repeated biopsies. The epithelial giant cells participated in the reaction of the surrounding mononuclear hepatocytes as it concerned alteration of endoplasmic reticulum, glycogen deposition and increase of lysosomes. They differed by excess amounts of acid phosphatase containing granules often filling the entire cytoplasm. On electron microscopy, dense, irregular bodies up to several microns in diameter were found which were not bile as described above. The nature of these presumably acid phosphatase containing granules is not established. They possibly represent enlarged lysosomes. Despite thorough search, no bodies of possible virus nature were demonstrated. On the border of the giant cells very few biliary microvilli were noted and histochemically little ATPase was seen. The microvilli facing the sinusoids were normal but the sinusoidal border consisted of half or more of the cell circumference on cross section. Frequently around the giant cells, an increase of collagen fibers was found. No evidence was obtained that the giant cells are degenerative cells. The investigations presented so far assist in the difficult differential diagnosis of neonatal jaundice particularly if fine structural techniques are applied. The presence of excess acid phosphatase associated with less accumulation of bile in vacuoles or in lakelike form and less bile canalicular dilation with microvillar changes in association with the known light microscopic observation of greater mesenchymal reaction supports the diagnosis of giant cell hepatitis in contrast to biliary atresia. The rare viral hepatitis of infancy differs by greater degree of cytoplasmic organelle alterations.

E. Hepatolenticular degeneration (Wilson's disease). In continuation of light microscopic examinations as to the specific character of the hepatocellular changes in Wilson's disease, eleven biopsy specimens of several stages were subjected to electron microscopic and histochemical examination as well as to immunocytochemical analysis. Even in milder stages without obvious light microscopic changes, the hepatocytes exhibited many dense lysosomes and pigment granules in the pericanalicular zone. The dense lysosome at least in part seemed to be formed by coalescence of granular material which entered the cell from the sinusoidal surface by pinocytosis. In contrast to lysosomes elsewhere those in the hepatocytes especially with pigment granules in Wilson's disease exhibited no acid phosphatase activity. This enzyme can be inhibited by copper *in vitro*, permitting the assumption that the acid phosphatase negative, dense lysosomes in Wilson's disease contain excess copper. In addition increased amounts of pigment apparently lipofuscin were noted. In the early stages studied other

organelles were not involved. Bile canaliculi revealed normal ATPase activity and biliary microvilli were normal. Sinusoidal alkaline phosphatase activity was increased. In a case in which one sibling had advanced liver disease, an asymptomatic one had a normal liver light microscopically, but absence of ceruloplasmin and increased hepatic copper and similar fine structural changes as the symptomatic patient. Immunocytochemical analysis for gamma globulin were as a rule negative. Thus the liver cell injury in Wilson's disease appears to be initiated by copper deposition in lysosomes and the usual self-perpetuation processes are not present, but progressive fibrosis is the result of liver cell injury. Correlation between the fine structural picture and clinical findings has not yet been possible.

F. Pigment accumulation. In view of the known relation of pigments to lysosomes and the possibility that pigment accumulation may be the result of faulty release from the lysosomes with resulting decreased excretion of the substance in the bile, studies on the nature, formation and disappearance of pigments are under way. Electron microscopically, the pigment formed following intravenous administration of fat emulsions to rats, appeared to be a collection of small but varying sized fat droplets in a vacuole surrounded by a single membrane. Similar pigment granules were seen in human livers in which presumably transitory fatty metamorphosis had occurred. These granules differed from lipofuscin pigment granules which are composed of lipid and nonlipid phases, all surrounded by a single membrane. Transitions of lysosomes to pigment granules were noted. Lipofuscin granules were characterized by intense acid phosphatase activity. Neither the lipofuscin pigment nor that following administration of fat emulsions resembled the pigment seen in chronic idiopathic jaundice (Dubin-Johnson syndrome). The latter was also surrounded by a single membrane but was much larger (5 to 10 microns in diameter) and irregular. The pigment granules noted in two patients with abnormal serotonin metabolism resembled most closely those appearing in animals following administration of intravenous fat emulsions. In hemochromatosis many lysosomes rich in lipofuscin pigment and acid phosphatase activity were noted which also contained dense particles of ferritin micelles, which in places fill them and even seemed to be spilling out of them. The present studies are so far descriptive and do not yet permit conclusions as to the relation between pigment and lysosomes, but point to the assumed relation between iron deposition and excess pigment formation.

G. Steatosis. Electron microscopic studies of livers with fatty metamorphosis in alcoholics and in patients with malabsorption or with Wilson's disease as well as in rats after high fat low protein feeding indicated compression of the cytoplasmic organelles without significant alterations. Some canaliculi appeared compressed but the biliary microvilli were not altered and the changes were not correlated with the presence of jaundice. This confirms previous observations of this laboratory that mitochondrial damage and ethionine induced hepatic fat accumulation are not necessarily related (6). This, however, does not exclude the possibility that excessive fat accumulation may secondarily lead to mitochondrial injury. Since this injury seems not to be a causative factor in hepatic

steatosis, the search for such factors continued. In view of the recently emphasized role of catecholamines in the development of steatosis, the derangement of the epinephrine metabolism in hepatic fatty metamorphosis induced by ethionine was studied. Epinephrine is converted to metanephrine by the liver enzyme catechole-methyl transferase, the methyl donor being *s*-adenosyl methionine formed from methionine and TEP. If methionine was replaced by ethionine the conversion of epinephrine to metanephrine *in vitro* did not occur since *s*-adenosyl ethionine is formed as a completing factor. *In vivo* the biologic half-life of injected epinephrine C-14 is longer in ethionine intoxicated rats than in controls, the excretion of epinephrine in both urine and bile being greatly reduced. Since the biologic half-life of metanephrine-C-14 was nearly identical in ethionine intoxicated and control rats, the limiting factor is the delayed transformation of epinephrine to metanephrine. In adrenalectomized cortisone or ethionine treated rats, the presence of epinephrine is essential for the development of steatosis. Replacement of epinephrine by metanephrine did not promote steatosis. Therefore, the epinephrine-metanephrine reaction is a true inactivation of epinephrine and the delayed inactivation of epinephrine in the presence of ethionine demonstrated *in vitro* and *in vivo* may be a factor in hepatic fat accumulation. The etiologic and pathologic aspects of hepatic steatosis have been reviewed (7).

HEPATIC MESENCHYMAL REACTION

Since injury of the hepatocyte similar to that of other epithelial cells is accompanied by an inflammatory reaction presumably in response to the liver cell injury, the nature of the nonhematic mesenchymal cells in the liver was studied by fine structural techniques particularly since this mesenchymal reaction is responsible for several factors important in the chronicity of liver disease. The attempt is made to present a subdivision of mesenchymal cells similar to recent endeavors in the nomenclature of immunologically competent cells and of hematic cells. The hepatic mesenchymal cells were characterized on functional indications (8). The sinusoids of the liver parenchyma differed from capillaries elsewhere including the capillaries in the portal spaces of the liver by the absence of a basement membrane as demonstrated so far in man, dog, rat or mouse. The separation between blood space and tissue space is thus formed only by the Kupffer cells which do not completely cover the tissue space. Between Kupffer cells small gaps are present through which particulate elements may pass from the blood stream to the tissue space thus facilitating a more intimate contact between hepatocytes and blood constituents. The resting Kupffer cells corresponding to endothelial lining cells had few phagosomes or other organelles in a flat but elongated cytoplasm. Activated Kupffer cells in a littoral position in the sinusoidal lumen contained many phagosomes and exhibited much acid phosphatase activity as evidence of active phagocytosis. The activity varied with the functional state of these cells (9). Counterparts of these cells were seen outside of the sinusoids as resting or activated tissue histiocytes. From another type of cell with little endoplasmic reticulum, a filamentous material seemed to stream from the cytoplasm. Outside of the cell membrane this became thicker

and showed the periodicity of collagen fibers. These fiber forming cells did not have the light microscopic appearance of fibroblasts which were not found within the parenchyma but only in portal spaces. Another irregularly shaped, heavily PAS positive cell contained small fragments of mature collagen fibers and was considered a fiber removing cell or "fibroclast." Finally cells were seen in either littoral position or outside sinusoids which contained occasional phagosomes but abundant endoplasmic reticulum and exhibited gamma globulin on immunocytochemical analysis. They are considered plasmacytoid cells though they resemble plasma cells only exceptionally.

REGENERATION

To separate transient regeneration associated with insult from regeneration persisting after discontinuation of insult, two groups of rats were fed methyl butter yellow for 26 and 40 days and sacrificed at intervals after discontinuation of the drug. After 26 days indications of the injury of the hepatocytes were hyaline inclusions, decreased basophilia and diminished glucose-6-phosphatase activity with minimal signs of regeneration. After 40 days many regenerative nodules with increased basophilia, mitosis and normal glucose-6-phosphatase activity were seen. With return to normal diets the regenerative nodules disappeared but other nodules appeared which were composed of hydropic cells with cytoplasmic PAS positive droplets and diminished glucose-6-phosphatase activity; they exhibited single cell necrosis. These latter nodules were larger in the 40 day group and became more prominent following discontinuation. Therefore these glucose-6-phosphatase free cells seem to represent an abnormal cell population not dependent on the presence of the offending drug which long before had been excreted (10).

INTERFERENCE OF BILE FLOW AND ROLE (FUNCTION OF THE DUCTULAR CELL)

The problem of intrahepatic cholestasis received added impetus by observations of Israeli observers as to the ability of alpha-naphthyl-isothiocyanate (ANIT) to experimentally produce this process by destruction of the epithelium of the small intrahepatic bile ducts. Chronic stages of the intoxication provided a model for the study of the function of the bile ductules to which, on the basis of electron microscopic studies, the ability was assigned to secrete water but not biliary substances (11). In confirmation of the Israeli investigations, 24 hours after feeding a single dose of ANIT necrosis of duct epithelium with plugging of the lumen by debris was noted. This was associated with considerable hyperbilirubinemia and with complete cessation of the bile flow. Relining of the ducts four days later was accompanied by return of bile flow and of serum bilirubin to normal range. In rats fed continuously for two weeks with smaller doses of ANIT, the wall of the septal bile ducts was tremendously thickened by edema and inflammation and it was surrounded by inflammatory exudate. The lumen appeared even more narrowed by heaping up lining epithelium. (The picture resembled that seen in an observed human case of jaundice following chlorpropamide administration.) Periportal parenchymal necroses in the rats were

considered the result of leakage of bile through injured ducts. This subacute stage was also associated with complete cessation of bile flow and unusually high bilirubin levels. Despite continued feeding of ANIT, the obstructive lesion regressed and bile flow and bilirubin returned to normal within several weeks. However, the bile flow rose again simultaneously with proliferation of bile ductules.

These late changes of the ANIT intoxication characterized by extensive ductular proliferation in the absence of liver cell necrosis were studied in contrast to other models in which ductular proliferation was present together with liver cell injury (subacute ethionine intoxication) or which showed liver cell injury with minimal or absent ductular cell proliferation (acute ethionine intoxication and subacute carbon tetrachloride or thioacetamide intoxication). In the presence of proliferation of ductules, the bile flow was increased three to four times with moderate increase in total amount but reduction of concentration of bile solids while in the absence of ductular cell proliferation a normal or decreased quantity of a dilute bile was secreted. The total amount of bile acid excreted was normal in the case of the ANIT intoxication and markedly reduced in the ethionine intoxication as reflection of hepatocellular injury. Since even in the ANIT intoxication, the biliary concentration of bile acids was low and the contribution to the bile solids was decreased from normal, the increased bile flow associated with ductular proliferation represented a hydrocholeresis. Since the increment represented excess fluid containing electrolyte and not biliary substances, it appears justified to assume that the microvilli of the bile ductules reflect secretion of an electrolyte containing fluid. This indicates, moreover, that ductular proliferation and periductular infiltration as seen in human cholangiolitis is not necessarily associated with cholestasis but rather may be accompanied by hydrocholeresis. A practical modification of the technique for demonstration of bile acids in the bile has been described (12).

In analogy to the above, one may also assume that the biliary microvilli of the hepatocytes reflect secretion of an electrolyte rich fluid while other biliary constituents are delivered by other hepatocellular organelles. Since bilirubin has been demonstrated in lysosomes and the latter together with the Golgi zone have been implicated in biliary secretion, the behaviour of acid phosphatase in the bile as a marker of lysosomes was studied. Hepatic serum and biliary acid phosphatases were investigated by electrophoretic, chromatographic and chemical analysis. Disc electrophoresis of acid phosphatases on polyacrylamide gels was worked out. By this technique as well as by anion exchange cellulose chromatography, four acid phosphatases were separated from rat liver. Rat bile exhibited considerable enzyme activity but chromatographically only one acid phosphatase could be identified in bile. Acid phosphatase activity and bilirubin concentration of the bile were directly related confirming further the role of lysosomes in the excretion of bile.

MECHANISM OF HEPATIC FIBROSIS

The effect of intrahepatic injection of the polygalactose carrageenin and of quartz was studied to separate the lesion produced by the transient stimulus of

carrageenin from the permanent one of quartz. Fiber formation occurred close to bile ductules and fibroblasts suggesting a stimulating effect of the proliferating ductular cell. Quartz produced a more violent initial reaction with predominance of segmented leukocytes and lack of macrophages. Cortisone altered the local hepatic fibrogenesis from carrageenin by increasing the necrosis, partially inhibiting proliferation of fibroblasts and ductular cells as well as the deposition of ground substance and reticulum fibers. Cortisone had no effect on local hepatic fibrogenesis induced by quartz (13). The morphologic effects of intrahepatic and subcutaneous injection of carrageenin were compared in normal and scorbutic guinea pigs, in the latter the coagulation necrosis produced was more severe and proliferation of ductular cells and fibroblasts as well as formation of argyrophilic fibers scanty. However, around the necrotic area abundant intensely PAS positive and alcian blue negative material was laid down which underwent partial calcification. At this time it cannot be decided whether the presented observations indicate a primary alteration of collagen forming cells or of the hydroxyproline proline interrelation (14). An electron microscopic study of hepatic fiber formation has been completed (15).

To study cellular factors, the ratio between hydroxyproline and DNA in the liver was found constant in a large variety of different conditions associated with fiber accumulation in the organ such as in subacute ethionine intoxication, in subacute carbon tetrachloride intoxication, in the effects of a high fat low protein diet, in chronic ANIT intoxication following bile duct ligation as well as in modifications and regressions of the subacute ethionine intoxication brought upon by cortisone or methionine. This indicated a close relation between fiber formation and cell proliferation (16). In ethionine intoxication, the proliferating ductular cell might be the stimulus while in other types of injury without ductular cell proliferation, the proliferating hepatocytes regenerating in response to liver injury might represent the stimulus.

These studies supplemented by radioautographic investigations have also permitted the demonstration that the excess protein and DNA found in many chronic hepatic injuries represented proliferating ductular cells pointing to the importance of histologic controls of chemical analyses (17).

Cellular, enzymatic and hormonal (see below) factors responsible for the disappearance of collagen are being further explored. Determination of the life span of ductular cells by tritiated thymidine and of collagen by proline C-14 during the recovery of the ethionine intoxication should indicate whether the rapid disappearance of collagen and ductular cells is caused by increased catabolic processes or by interference with new formation. Electron microscopic examinations carried out so far seem to favor the former as far as the ductules are concerned.

In investigations on cirrhosis, emphasis has been laid upon demonstration of the pathogenesis of the cirrhosis in alcoholics, of hepatic schistosomiasis, and of the process associated with self-perpetuation. Some of the latter two problems will be dealt with in the subsequent section on immunology (see below). The transformation of portal cirrhosis into postnecrotic cirrhosis of the alcoholic has been investigated (18) using semiquantitative histologic evaluation of the

cardinal features of each type of cirrhosis. It was found that as the disease progresses, the features of alcoholic portal cirrhosis, *i.e.* fat and alcoholic hyaline, decreased while the features of postnecrotic cirrhosis, namely multilobular nodules, collapse and variation in size and shape of nodules, increased (19). It was concluded that in alcoholics postnecrotic cirrhosis is frequently the end result of a chronic hyperplastic response to continuing necrosis which originates in the classical monolobular septal or portal cirrhosis of alcoholics.

EFFECT OF STEROIDS ON HEPATIC INJURY

The effect of cortisone was studied by histologic, radioautographic, cytochemical and electron microscopic procedures during two stages of the subacute ethionine intoxication. One represented the "florid" phase present in rats which have been from 5 to 7 weeks on a synthetic diet containing 0.5% ethionine. During this stage fibers accumulated, various enzymatic activities decreased and cell proliferation took place. The last was reflected in excessive accumulation of ductular cells and slight increase of mesenchymal cells as demonstrated by cell counts. The new formation of ductular cells was also demonstrated by radioautographic determination of the distribution of cells labeled with tritiated thymidine and by total thymidine-H3 uptake. Total hepatic protein, DNA and hydroxyproline also steeply increased. Cortisone treatment in this stage arrested but did not reverse these changes apparently by promoting an equilibrium between anabolism and catabolism of ductular cells and fibers. The decreased enzyme activities were restored to normal possibly because of an effect on hepatocytes (20). Electron microscopically cortisone given after five weeks reversed existing mitochondrial swelling without the mitochondria being entirely normal after two weeks. Endoplasmic reticulum in some of the cells became rich and granular. The earlier the therapy was started and the longer it was given, the more of this type of endoplasmic reticulum was found. The hepatocytes contained numerous pigment granules which were typical lipofuscin. The ductular cells showed cytoplasmic disintegration and extrusion of cytoplasm into the lumen. Treatment with methionine had a similar effect at this stage except no pigment accumulated. In contrast in the "stationary" phase of the intoxication, no further alteration of the mentioned parameters including the electron microscopic picture was noted. This might offer analogies to the treatment of human liver diseases by steroids. Studies in progress indicated that adrenalectomy inhibits the methionine-induced recovery after subacute ethionine intoxication reflected in disappearance of ductular cells and fibers and that total adrenal extract but not cortisone is able to reestablish this recovery. In contrast to corticosteroids, anabolic steroids have been shown in previous investigation to have an icterogenic effect. In man and rats given norethandrolone, canalicular dilatation and changes of biliary microvilli were described even in the absence of jaundice. Several analogs of norethandrolone are being investigated for the same effect to ascertain the chemical nature of the steroid associated with the structural change.

IMMUNOLOGICAL STUDIES IN LIVER DISEASE

In continuation of previous investigations, the distribution of gamma globulin in the liver was studied by immunocytochemical techniques, particularly to elicit the significance of this distribution and to identify the lesion with which it is associated. In primary biliary cirrhosis most of the gamma globulin demonstrated histologically was macroglobulin rather than the common S₇ globulin. Since it was possible to demonstrate fibrinogen, albumin and other plasma proteins together with gamma globulins in hepatic mesenchymal cells in hepatitis, it was assumed that this deposition is the result of phagocytosis. In contrast, in all types of cirrhosis only gamma globulin could be demonstrated in basophilic mesenchymal cells, indicating local formation of gamma globulin. The gamma globulin was not eluted at a pH 3.2, suggesting that it was not part of an antigen-antibody complex. The distribution of the gamma globulin showed no relation to ischemic or biliary necrosis, nor to the injury characteristic of alcoholics as indicated by Mallory's alcoholic hyaline. It did, however, correlate with "piecemeal necrosis," which is characterized by loss of hepatocytes on the periphery of lobules and nodules associated with local accumulation of lymphocytes, plasma cells and histiocytes and proliferation of bile ductules (21). This type of necrosis had, in previous statistical studies based on biopsy material, been identified as the morphologic expression of the progression of cirrhosis, independent of its etiology. The presence of gamma globulin containing mesenchymal cells in piecemeal necrosis pointed to an immunologic phenomenon, with the antigen being in question. Therefore, an hepatic lesion was studied with a known antigen, namely schistosomiasis. In experimental schistosomiasis of mice, gamma globulin was demonstrated in Kupffer cells and histiocytes around the granulomas as well as in the necrotic zones, in the latter apparently as antigen-antibody complexes. Serum of patients with active schistosomiasis was found to bind specifically by immunocytochemical techniques to adult worms and ova as well as to products of the latter and to the antigen-antibody complexes in the necrotic areas. These observations provided a technique for serum diagnosis of schistosomiasis with known tissue and for tissue diagnosis with known sera. It also represented a model for conditions in which the antigen was unknown (22). Therefore, the attempt was made to establish binding of serum of patients with various liver diseases to liver tissue by similar immunocytochemical methods. Sera of patients with very active viral hepatitis and with primary biliary cirrhosis showed neither organ nor species specific binding to nuclei similar to sera of patients with lupus erythematosus. It was destroyed by antecedent treatment of the tissue with DNAase. This binding which was not associated with positive L.E. reaction was considered a reflection of mesenchymal hyperactivity without apparent pathogenetic significance. Patients with a variety of active liver diseases showed also binding to proliferated bile ductules and their contents. The material thus indicated gave a positive PAS reaction (23). It appears therefore that in patients with liver disease carbohydrate containing antigenic material is excreted in the bile, which stimulates the formation of circulating antibodies. A pathogenetic action of this antibody itself appeared improbable, but in view

of the finding of antigen/antibody complexes in the necrotic areas of schistosoma granulomas and the recently emphasized cytotoxic effect of antigen/antibody complexes, the hypothesis is being entertained that such complexes in or around the bile ductules have a cytotoxic effect leading to piecemeal necrosis (24). To support this hypothesis, two types of known antigen/antibody complexes dissolved in excess antigen were injected retrograde into the bile duct of rats. They produced periportal acute and chronic lesions not elicited if either antigen or antibody were injected alone.

The presence of immunologic reactions in schistosomiasis stimulated the study of advanced instances of human hepatic schistosomiasis from Brazil. Changes characteristic of postnecrotic cirrhosis and of an active chronic hepatitis were found in high incidence, in contrast to the material usually seen in this country or in Puerto Rico. The cirrhotic lesions were considered the result of repeated ischemic insults from esophageal variceal hemorrhage tolerated better than in other types of cirrhosis. However, also piecemeal necrosis was noted, possibly as an expression of a chronic immunologic response either to schistosomal antigen or to liver cell breakdown products (25). The availability of material of experimental mouse schistosomiasis encouraged a histochemical analysis. Acid phosphatase, 5-nucleotidase, ATPase, amino peptidase, alkaline phosphatase were demonstrated in the schistosomal ova in addition to complex carbohydrate which is probably the main antigenic component. The granulomatous tissue around the ova displayed histochemical reactions characteristic of chronic proliferative inflammation (26).

Attempts at producing permanent hepatic lesions with Freund's adjuvant mixed with hepatic tissue did not succeed nor did the admixture of liver tissue alter significantly the initial lesion (27).

As a supplement to the immunologic studies serum proteins in liver disease have been investigated by disc electrophoresis (28).

DUCTULAR CELL REACTION

Many of the observations presented throw light on a phenomenon found in many chronic hepatic conditions, namely, the ductular cell reaction which implies proliferation of bile ductules with associated inflammation. This lesion is considered a response of the liver to injury presumably associated with biliary excretion of a material which stimulates ductular proliferation resulting in excessive flow of a diluted bile and in periductular inflammation. The latter if protracted leads to hepatic fibrosis with the proliferation of the ductules providing a stimulus for fibroplastic cells to form fibers as well as a mechanical anchor for these fibers. The possibility that the hypothetical irritant is of carbohydrate character and antigenic is raised. The material in the periductular tissue not being readily metabolized may stimulate antibody formation and might subsequently participate in locally cytotoxic antigen/antibody complexes. The ductular cell reaction appears therefore to favor chronicity of liver disease by dissemination of mesenchymal cell activity throughout the organ. Future investigations are therefore focused on the immunologic identification

of the supposed antigen and on the chemical identification of the carbohydrate compounds.

SUMMARY

Various types of acute hepatic injury and the processes leading to and associated with hepatic fibrosis and cirrhosis were studied by fine structural and biochemical techniques. In subacute ethionine intoxication of the rat and in human viral hepatitis, the emphasis was laid on alterations of the endoplasmic reticulum. In cholestasis, alterations of biliary microvilli were followed by changes in other cytoplasmic organelles. In giant cell hepatitis of infancy, excess acid phosphatase distribution is conspicuous while in Wilson's disease a lysosomal alteration had been demonstrated. Hepatic steatosis in acute ethionine intoxication was associated with impairment of the catecholamine metabolism. The hepatic mesenchymal cells in part developing in response to liver injury were subdivided on a functional basis. Proliferation of bile ductules was found associated with hydrocholeresis instead of with biliary obstruction suggesting that these cells secrete an electrolyte rich fluid. Steroid therapy influences the "florid" but not the later "stationary" phase of subacute ethionine intoxication. A constant relation between hepatic hydroxyproline and DNA in various conditions with hepatic fibrosis suggests a role of cell proliferation in fiber formation. Immunologic studies demonstrated peripheral piecemeal necrosis of the liver as a condition associated with local formation of gamma globulin, indicated an antigen excreted in the bile in patients with active liver disease, suggested a role of antigen-antibody complexes at least in experimental liver injury and pointed to immunologic reactions in schistosomiasis. Ductular cell proliferation with associated inflammation is a mechanism leading to chronicity in liver disease.

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A CHLORPROMAZINE ORGANIC PSYCHOTIC REACTION

RAY S. GREENBERG, M.D. AND EDWARD D. JOSEPH, M.D.

New York, N. Y.

With the widespread use of tranquilizers in medical and psychiatric practice, many untoward and often undesirable effects of the drugs have been reported. Frequently observed physiologic side effects include drowsiness, skin eruptions, Parkinson-like syndromes, dystonias, akathisias, and, less commonly, agranulocytosis and hepatic damage. Psychotic reactions with the use of tranquilizers have only occasionally been reported. Berry, *et al.* described two children who had cataleptoid states following administration of perphenazine (Trilafon) (1). The drug was given to one child for hypochondriacal somatic complaints and to the other child for excessive vomiting associated with an upper respiratory infection. In both cases the cataleptoid states subsided after the drug was discontinued. May reported two psychotic patients in whom cataleptic states developed after they received promazine (Sparine) and prochlorperazine (Compazine) respectively (2). Both patients reverted to their previous psychotic states with disappearance of the cataleptic states after the drugs were discontinued and the use of Congentin was instituted.

Recently, Lang and Moore reported an organic psychosis with neurological changes following chlorpromazine therapy in a patient previously not overtly psychotic (3). This appears to be the first report of such a complication. Their patient's initial symptoms were anxiety, dizziness, palpitations, and fear that he would be unable to breathe or that his heart would stop. After three doses of chlorpromazine, totaling 75 mg, the patient complained of palpitations and panic, and said he felt "like an empty shell, floating around in the air." The chlorpromazine was increased to 50 mg four times a day and the patient experienced auditory hallucinations which he felt came from two men standing on his chest. Two days later he had neurological symptoms of dysarthria, dysphagia, diplopia, ataxia, and coarse tremors. The organic psychosis and neurological symptoms cleared within a week after chlorpromazine was discontinued and therapy with intravenous Amigen, potassium, premethazine, multivitamins, dilantin, and phenobarbital was instituted.

The following case is of interest not only because of the organic psychosis that occurred concurrent with the use of chlorpromazine, but also because of the role that the drug reaction seemed to play in the remission of symptoms.

CASE REPORT

D.D., a 57 year old housewife, was referred by the neurology service to the psychiatric service because of severe, incapacitating pain in her neck, radiating down her left arm. No organic cause could be found for this pain.

From the Department of Psychiatry, The Mount Sinai Hospital, New York, N. Y.

Four months prior to admission, the patient was preparing for the wedding of her niece, the daughter of a favorite stepbrother who had died some years ago. On the day of the wedding she felt as if she could not stand up. Her family doctor diagnosed her illness as "intestinal gripe" and the patient went to bed. Two days later, there was a hurricane and the rain came into the windows of her apartment. The patient's husband was at work, and although there was a maid in the house, she got out of bed to mop up the water. While wringing out a heavy rug, she had a sharp pain in her neck and left arm, with a sensation of paralysis in the arm. In spite of muscle relaxants, prochlorperazine, meprobamate, analgesics, and chlorpromazine 100 mg four times a day prescribed by her family doctor, the pain continued. She rapidly withdrew from her social activities, neglected her home and her person, and became irritable, anorexic and insomniac. She was admitted to the neurology service, but neurological examinations, including a myelogram, did not establish an organic cause of the pain.

On admission to the psychiatric service, the patient weighed 96 pounds although she was of average height. She was pale and untidy, wore no make-up, had not combed her hair and appeared at least ten years older than her stated age. Her facial expression was sad and self-pitying, and she moaned and cried almost continuously. She was querulous and demanding, finding fault with the location of her bed, the menu, the temperature of the food, the ward routine, and she was dissatisfied with every offer of help by the nurses and doctors. She walked with small steps, her back hunched over, and her right hand holding her left arm which was flexed and held close to her body. There was moderate atrophy of the muscles of the left arm and hand, marked limitation of active motion, but no limitation of passive motion. The sensorium was clear and no hallucinations or delusions were elicited. Psychological tests indicated a mixed neurotic pattern with compulsive defenses, conversion symptoms and depression.

Nine years previously the patient had her first attack of cervical pain. At that time she was having her hair washed in a beauty parlor, and while sitting with her head extended, she suddenly felt a sharp pain in the back of her neck; the pain radiated to both shoulders and arms and down her back to the lumbar region. Straightening the trunk relieved the pain temporarily, but it quickly returned and persisted in the neck and left arm. A diagnosis of slipped cervical disc was made. Treatment with collar traction, x-rays, head traction, and local injections of procaine relieved the pain for brief periods only. Weakness and atrophy of the left palm developed. The diagnosis was confirmed by myelogram and hemilaminectomy was performed on the neurology service of The Mount Sinai Hospital. There was marked improvement of objective neurological findings, but the pain persisted in spite of increasing doses of Demerol and codeine. The patient became depressed and talked of not wanting to live.

She was transferred to the psychiatric service, where she was seen in daily psychotherapy sessions. Her pain persisted, and after three months of psychotherapy and her continued demands for increasing amounts of Demerol, she was given twenty electroshock treatments. Except for a mild organic mental state

following convulsive therapy, her condition remained unchanged. It was decided to give her Demerol on a demand basis, and in one week she went up to 2000 mg per day. The patient said she thought that allowing her to have Demerol in this way meant that she was hopeless. She then was seen twice a day in psychotherapy, had a special nurse, and was treated with muscle relaxants. Her demands for Demerol were reduced until she discontinued its use, and with the help of suggestive therapy, she improved and returned to her former life.

Six years later the patient and her husband were in an automobile accident; the patient was unhurt, but the husband, on physical examination, had evidence of a past "silent coronary." Shortly after this discovery, the patient had an attack of pain in her neck and left arm after pushing some heavy furniture at home. This attack subsided spontaneously. The patient remained busy and asymptomatic until the present episode.

History

When the patient was four months old, her mother died of unknown causes. The father remarried soon after, so that the patient considered her stepmother to be her real mother until she was informed of the true facts at 14 years of age. She felt close and affectionate towards her stepmother. The patient played mostly with boys and felt closest to her youngest stepbrother. She was a bright student, and, although for financial reasons she had to begin working when she was 15, she attended night school and received a high school diploma. At the age of 16, she met her future husband, to whom she was attracted because he seemed neat and clean and did not try to kiss her.

She married at 21, and claimed her first sexual instruction was given to her by her husband. In most respects, the marriage was a happy one. There were two children, a daughter and a son, who, although unplanned, were treated with warmth and pride by the parents. The couple had an active social life, with many friends and numerous trips to vacation resorts. The patient was a perfectionistic housekeeper who enjoyed entertaining. Sexually, however, there were difficulties from the beginning. The husband initially had premature ejaculation; later he attempted to adjust his activity to the patient's desires. The patient remained frigid, and became increasingly reluctant to have intercourse. Eventually they slept in separate rooms.

When the patient was 37 years old, her stepmother died of cancer of the breast. When the patient was 45, her favorite stepbrother, the youngest, died suddenly following a herniorrhaphy. The patient was at the stepbrother's home, helping his wife, when she was called to the hospital. She arrived after the brother had expired, to her intense regret. The next year, her father, who had Buerger's disease, died of a coronary thrombosis.

Nine years ago, shortly before the patient's first attack of cervical pain, her daughter married and moved to another state. When the patient was discharged from the hospital after her treatment for that episode, her daughter and son-in-law returned to live with her for a year.

Hospital Course

During her present admission to the psychiatric service she was initially put on a self-demand schedule, using all the medications she had been taking, including chlorpromazine 100 mg four times a day, eating whatever and whenever she wanted, and as many of her requests as practicable were fulfilled; nevertheless, her condition remained the same. Two weeks later, there was a change to a female therapist, to whom the patient related as if to a daughter; for example, she gave the therapist advice on housekeeping, cooking, and the care of children. She consistently denied hostile feelings towards anyone, and spoke of the significant people of her life in euphemistic terms. She expressed concern for her husband in view of his history of a "silent coronary" and felt relieved each night when he appeared.

Because of the depressive features, chlorpromazine was discontinued, the other drugs were tapered off, and she was given imipramine (Tofranil) 50 mg three times a day. Psychotherapy was superficial and supportive, as it was felt that the patient was not approachable in terms of insight therapy. During the first week of this regimen, the patient became more sociable, complained less of pain, began to help with ward cleaning, slept better, showed improved appetite, gained weight, and accepted the withdrawal of her other drugs.

She commented to her husband one evening that she wanted to be out of the hospital in time to prepare meals for the family for the forthcoming religious holiday. Her husband replied that he would not let her do such work, as she was too sick. The next morning the patient again stayed in bed, and rapidly deteriorated to the point where she did not eat or sleep, cried out in pain day and night, trembled, and held her arm tightly to her body. She finally became uncommunicative except to say that she had so much pain, she wanted to die. She brushed aside any connection between her husband's comment and the immediate relapse to her former state.

All her previous medications were discontinued, and she was given 300 mg of chlorpromazine four times a day. She became quieter, but on the second night of this regimen, she got out of bed and complained to the nurse that there were rats in her bed. She told the nurse to come see the Mexican ants on her pillow and the dog in her bed. She complained that there was a boy in the next bed bothering her with a pencil and paper. She could hear her husband's voice and was frightened because he was talking about taking her to a mental hospital. The next morning she told the therapist that she could still see ants on the pillow and that the nurse would not do anything about it; she demanded that the pillow-case be changed. She was confused and disoriented about the time and place. Chlorpromazine was reduced to 200 mg four times a day, and within one day the hallucinations ceased, the sensorium cleared, and she said the pain had entirely disappeared. She had excellent motion in her left arm and used it freely. Of the events of the previous three days, she recalled only that she had felt she would get better or die. She had a good appetite, became neat, pleasant, cheerful, slept better and rapidly gained weight. She was discharged asymptomatic on 500 mg chlorpromazine a day within three weeks.

DISCUSSION

An attempt to understand the patient's particular response to treatment also involves an understanding of the development of symptoms initially and on the two subsequent occasions.

The original onset of pain was undoubtedly due to an organic disorder. Once the organic pathway was established, however, the patient utilized the affected area for the discharge of her emotional conflicts and reactions. This was observed when the hemilaminectomy relieved all objective neurological signs, but the pain remained unabated. Later episodes of pain were associated with emotionally tinged situations. This psychological mechanism was confirmed during the present attack of pain, when disuse atrophy of the musculature of the left arm was the only objective sign of disorder.

The recent attack of pain must have been associated with fear for her husband who was away from home during the storm. Her concern for him, related to his "silent coronary," was probably related to fear of losing him as she had lost her father from a heart attack. She probably experienced anger at her husband for not being at home with her during the storm; she was afraid, and, sick in bed, needed help. With the patient's denial of all hostile feelings, the resultant conflict was then converted into physiologic pain and paralysis of the arm. This occurred immediately after her reaction to her niece's wedding, which would have acutely recalled the loss of her favorite younger stepbrother and the guilt she felt at not being with him when he died. The indirect expression of hostility through irritability, crying loudly of pain, and inattention to her daily duties, was observed again in her response in the hospital to the frustration of her plans to prepare meals for the religious holiday.

The patient's brief improvement during her third week of hospitalization, when the female therapist took over her care indicated that a psychological alteration was already taking place, probably related to her particular transference relationship to the therapist. This may have been a reactivation of her feelings connected with her daughter's returning to live with her following her first hospitalization.

The striking change in the patient following the period of high dosage of chlorpromazine requires exploration. The confused sensorium and visual content of her hallucinations experienced during the two day period were of an organic type indicating a toxic psychosis. It is unlikely that the reaction was one of sensitivity, since there was no observable response to the 400 mg a day of chlorpromazine which the patient received during the initial phase of treatment. The high dosage of chlorpromazine (*i.e.*, 1200 mg per day), however, was administered at a time when the patient was debilitated and dehydrated, a condition probably contributing to the subsequent overwhelming intoxication. Evidently her threshold lay between 800 mg per day, which produced no symptoms, and the 1200 mg per day which did lead to the organic psychosis.

On this occasion the toxic state was followed by striking recovery from her symptoms, in contrast to the patient's lack of response to the twenty electro-

shock treatments during her previous hospitalization. This behavior suggests that it was not the organic condition per se that promoted improvement.

Similar to the patient's use of a pathway of organic disorder for the expression of emotional conflicts in the development of symptoms, it is possible that some inner conflicts were discharged or "resolved" during her state of organic confusion. A clue to the nature of the conflict can be seen in the content of the hallucinations. Bugs and rats often are symbolic of siblings. The boy in the next bed and perhaps the dog in the patient's bed might have represented the patient's stepbrother who was thus "revived." Equally, the patient's recollection of the toxic period as a time when she would get better or die suggests that she experienced the events as a rebirth phenomenon. One wonders if the patient fantasied this period as a threat to her life and sanity, and consequently gathered her ultimate resources. The profound disability may have gratified masochistic drives which had been reflected in her anorexia, dissatisfaction with offers of help, and her martyred and self-pitying attitudes. There may even have been a reenactment of fantasies of her mother dying and a new mother appearing. The ministrations of the therapist during this time may again have represented the return of the daughter.

Another thought stimulated by this patient is concerned with the nature of pain, pain mechanisms and pain pathways to the central nervous system. There was no doubt in the mind of anyone who saw this woman during any of her acute periods that she was suffering extreme physical pain as well as mental anguish (4). The nature and origin of this pain is unclear. No physical basis could be found. The role of her pain as an expression of her suffering, as a protest against the environment, and as a plea to be taken care of by those around her, is evident enough. But how the pain is generated and maintained remains uncertain. It is another form of the "mysterious leap from the mind to the body." The clinical picture that this patient's pain suggests is that of a "phantom limb" syndrome. In that condition the origin of the pain is also unknown, but it is clear that the unconscious mental image of the missing member is invested with sufficient energy to overcome the conscious knowledge of its absence. This patient, of course, did not have a missing limb, but the mechanism of pain production may have been the same.

As a corollary to this, the action of the drug in controlling this symptom remains unclear. Does the drug work on peripheral pathways? Does it exert its action on some level of the central nervous system? Or, is its action indirectly indicated through its effect on mental function which, in turn, obviates the need for such a symptom? Or, finally, was its pharmacologic effect enhanced by the relationship to the doctor who prescribed the drug?

SUMMARY

An organic psychosis following chlorpromazine therapy provided an area for discharge of conflictual material in a patient who utilized an area of previous physically-determined pain for expression of emotional reactions. Within a stage of transference to the therapist, the patient reintegrated, and there was a remission of symptoms.

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Clinico-Pathological Conference

THROMBOCYTOPENIA WITH GANGRENE OF LEG AND WRIST DROP

Edited by

FENTON SCHAFFNER, M.D.

New York, N. Y.

A 57 year old man, a jeweler, was admitted to The Mount Sinai Hospital for the second time, complaining of pain and swelling of the right leg for four days.

On his first admission, three years earlier, the patient entered the hospital because of ankle edema of six days' duration. He learned he had mild hypertension 18 months earlier which was said to have subsided. Later he was told he had small amounts of sugar in his urine which was checked because his brother was a diabetic. Two months prior to admission he had a productive cough and x-ray revealed fluid in his chest. This was not treated and one week before admission he noted increasing abdominal girth, scrotal swelling and ankle edema. He lost five pounds after the injection of a mercurial diuretic. He had no history of rheumatic fever, arthralgias, chest pain or shortness of breath.

He was afebrile with a pulse of 130/min and blood pressure 160/90. He was slightly dyspneic and had a mild cough. In his ocular fundi some arteriolar narrowing, capillary aneurysms and many waxy exudates were seen. Bilateral pleural effusion was present, more on the right than on the left, with a few rales above the area of dullness. The PMI was prominent at 11 cm to the left of the midsternal line in the 5th interspace. The rhythm was sinus tachycardia. A mid-diastolic gallop and muffled tones were heard at the apex. No murmurs were detected. The neck veins were distended and pulsatile when he was upright. Hepatojugular reflux was demonstrated. Shifting dullness was present in the abdomen and the liver edge was down 3 fingerbreadths. He had hyperesthesia and decreased vibratory sense in both feet. Scrotal swelling and 3+ ankle edema were present. The left ulnar and both dorsalis pedis pulses were diminished but palpable.

Some laboratory data are summarized in Table I. Sedimentation rate was 8 mm/hr., BUN 14 mg%, blood sugar 123 mg%, albumin 3.7 Gm% and globulin 3.7 Gm%. Electrolytes were normal and the serology was negative. The pleural fluid contained 790 RBC/mm³ and 270 WBC/mm³ with 8% segmented leukocytes, 80% lymphocytes, 12% large mononuclear cells and occasional multinuclear cells. Chest x-ray showed bilateral pleural effusion, prominence of vessels, no pulmonary infiltration and moderate enlargement of the heart. Electrocardio-

From the Department of Pathology, The Mount Sinai Hospital, New York, N.Y.

gram indicated a right bundle branch block with a Q wave, depressed ST segment and inverted T wave in V_1-V_4 (Fig. 1).

Following digitalization, mercurial diuretics and right thoracentesis with removal of 1.5 liters of fluid, the patient lost 27 pounds. He was normotensive in

TABLE I
Hematologic Data and Results of Urinalysis

	1st admission	2nd admission					
		1st day	7th day	14th day	17th day	20th day	23rd day
<i>Urine</i>							
Spec. grav.	1.016	1.010	1.004	1.014	1.024	—	—
Albumin	0	ft. tr.	0	2+	0	—	—
Sugar	3+	0	0	tr.	0	—	—
Red blood cells	0	2-3	0	rare	0	—	—
White blood cells	0	1-2	occ.	1-2	occ.	—	—
Casts	0	2-3 hyal.	0	rare gran.	0	—	—
<i>Blood</i>							
Hemoglobin (Gm %)	14.8	12.7	10.6	11.2	10.9	9.6	11.4
RBC/mm ³ × 10 ⁶	—	—	—	—	—	3.79	4.05
Platelets/mm ³	—	—	170,000	—	—	96,000	52,000
WBC/mm ³	9,800	9,600	9,100	29,100	24,000	30,900*	40,500*
Segmented (%)	66	72	77	86	79	83	67
Bands (%)	12	3	0	7	12	6	15
Lymphs (%)	16	20	14	2	8	1	5
Monos. (%)	4	3	5	5	3	6	7
Eosin. (%)	2	2	4	0	0	0	1
Immature (%)	0	0	0	0	0	4	5

* In these smears, blast forms, immature leukocytes, atypical lymphocytes, normoblasts, reticulocytes, bizarre and giant platelets and occasional macrophages were seen.

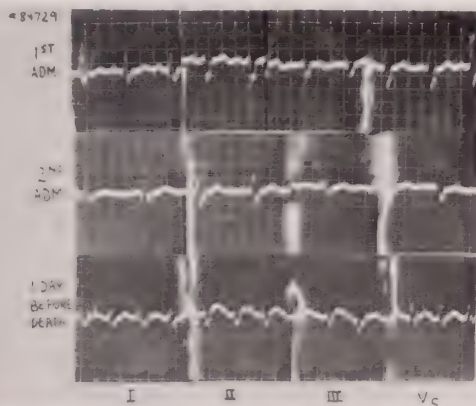


FIG. 1. Electrocardiograms taken early during both hospital admissions and just prior to death.

normal sinus rhythm and the gallop disappeared. The patient was discharged on the 11th hospital day.

The patient was maintained on digitalis and chlorothiazide without symptoms for three years and he continued to work. A week before his second admission he noted pains in his right lower extremity and three days later it became swollen, dusky and more tender.

Vital signs were normal. Occasional crackling rales were heard in the lung bases. A soft systolic murmur was heard at the apex but the heart was not enlarged. The liver edge was felt just below the costal margin. The right leg was dusky and bluish and was almost twice as large as the left one. The swelling involved the entire extremity. A red tender cord was visible, palpable and tender along the right long saphenous vein.

Some of the laboratory data are in Table I. The sedimentation rate was 29 mm/hr., BUN 17 mg%, blood sugar 109 mg% and serum cholesterol 200 mg%. Prothrombin time was 24.5 sec. with a control of 13 sec. An electrocardiogram was unchanged from three years previously (Fig. 1).

The patient was given Coumadin, Butazolidin and soaks for the leg. The patient seemed quite sensitive to the anticoagulant and had to be given vitamin K several times because of greatly prolonged prothrombin times. Anticoagulation was continued for two weeks. After discontinuation the prothrombin time ranged between 20 and 22 sec. The inflammation in the right leg quickly subsided and then the edema lessened. On the 12th hospital day the patient's right lower leg became cyanotic and cold. Despite vasodilators and a paravertebral block, gangrene developed with a line of demarcation just above the ankle. The right popliteal pulse was diminished and no pulses were felt below this. The patient became febrile, toxic and somewhat disoriented during the next ten days. Swelling of the left foot became apparent. On the 20th hospital day he lost control of his left hand and forearm with a wrist drop although sensations were normal. No other neurologic abnormalities were present. This cleared somewhat in two days but then the patient began vomiting, became clammy and his blood pressure dropped. Electrocardiogram showed R to be smaller in 2, 3 and aVF. ST elevated in 2, 3, V₅ and V₆, and depressed in aVL and T diphasic in V₃ and taller in V₅ and V₆ (Fig. 1). He became disoriented, his pupils did not move to the right of the midline and he had severe paresis of both upper extremities. This progressed to flaccid paralysis, muscular twitching, Cheyne-Stokes respirations and shock marked his last two days of life. He expired on the 23rd hospital day.

*Dr. Sol Silver**: This very interesting clinical problem can be divided into two parts, which correspond to the patient's two hospital admissions. The patient had mild hypertension and diabetes. He had congestive heart failure manifested by enlargement of his abdomen, edema, and scrotal swelling. At this point the question seems to be to establish an etiology for his congestive failure. A tricuspid insufficiency, probably functional, can be assumed on the basis of the pulsating neck veins. The laboratory data are of little help in establishing a diagnosis. It might be wiser now to see the x-rays.

* Attending Physician, The Mount Sinai Hospital, New York.

*Dr. Mansho T. Khilnani**: Chest x-ray showed no infiltration on either side. Hilar and mediastinal structures appeared normal. A small amount of exudate was present on both right and left sides. The heart was slightly enlarged but had no specific configuration.

Dr. Silver: This in itself is quite unusual. It is uncommon for a man in such congestive failure that he has pulsating neck veins, to have a chest film with relatively trivial enlargement of the heart and no evidence of congestion in the pulmonary fields. The electrocardiogram should now be discussed.

*Dr. Leslie Kuhn***: The electrocardiographic findings were those of right bundle branch block pattern, but in addition, the Q waves in V_1 , V_2 and V_3 were abnormal even in an individual with a right bundle branch block. Inasmuch as the septum generally is excited from left to right, usually a Q wave is not present in the right side chest leads. The most likely diagnosis would be an old anteroseptal myocardial infarction. However, such findings as the Q waves in the septal leads have been described with rarer conditions. Those include massive hypertrophy of the right atrium and diffuse severe myocardial involvement with other than ischemic heart disease.

Dr. Silver: On the basis of this, there is no evidence of a recent acute coronary thrombosis with myocardial infarction?

Dr. Kuhn: The age would be difficult to tell but I would say probably not recent. This is more indicative of old anteroseptal myocardial infarction.

Dr. Silver: This extreme degree of heart failure apparently cleared up and remained absent for three years. With relatively simple therapy he went three years without further therapy. When he died, he had a heart of normal size, at least from the statement in the protocol.

This, then, is one of the forms of so-called reversible heart disease. There are many types of this, some of which he obviously did not have. He did not have anemic heart disease. He did not have thyrotoxic heart disease. He did not have heart disease due to arteriovenous aneurysm.

If a man has an acute coronary thrombosis, he can be in severe congestive failure and then do well, but we have very little evidence here either from the history or from the laboratory evidence to make a diagnosis of an acute myocardial infarction.

One type of lesion that could put a considerable strain on the right side of the heart and then resolve to a certain extent is pulmonary embolization. If a man had multiple pulmonary emboli, he could have severe right heart strain, and it is conceivable that this could get better.

This man did have chest pain and bilateral pleural effusions. This is a possible explanation for the episode three years before his admission. It is not clear whether the pleural fluid was an exudate or transudate. Some multinuclear cells were found in it but if a man had carcinoma of the pleura giving rise to multinuclear cells, he would not stay well after that without any recurrence of the pleural effusion. I am willing to dismiss carcinoma as the cause of the pleural effusions.

* Research Associate in Radiology, The Mount Sinai Hospital, New York.

** Assistant Attending Physician for Cardiology, The Mount Sinai Hospital, New York.

He came back three years later because of a new syndrome, which was an obvious acute thrombophlebitis of his left extremity.

This raises the question whether he could possibly have had thrombi in the veins during the previous admission.

He had a peculiar type of thrombophlebitis because he had a purplish markedly swollen leg. This is a syndrome called phlegmasia corulea dolens. There is a tremendous amount of blood trapped in the lower extremity as part of this thrombosis, and almost always implies rather massive thromboses of the deeper veins with perivenous lymphatic involvement.

His leg seemed to be improving when gangrene developed. Gangrene in this type of blue phlegmasia is part of the picture. It can occur as a pure venous gangrene without direct involvement of the arterial trunks or it can occur with involvement of the arterial trunks, either by spasm or by occlusive disease.

The pulsations were reported as diminished below the popliteal region, but in a leg markedly distended, it might be difficult to elicit pulsations, and an element of arterial spasm is usually present.

The fact that his heart was not enlarged three years after his previous episode rules out a primary cardiac disorder in this patient, especially when coupled with relatively slight changes in the electrocardiogram.

Dr. Kuhn: The electrocardiogram at this time was unchanged compared to the first record. There were two subsequent recordings, and both of them were unchanged. His final electrocardiogram shortly before death shows that they were most significant in leads III and aVF in which there was a slight diminution of the R wave and an elevation of the ST segments. The old right bundle branch block pattern with Q waves in the septal leads was maintained. The interpretation of these changes was not entirely clear since the R waves diminished somewhat and there was ST elevation in II, III and aVF. The most likely diagnosis electrocardiographically would be acute diaphragmatic wall myocardial infarction.

However, it is entirely possible that these changes represent ischemia of that surface and not infarction.

Dr. Silver: He came back with gangrene and then had a bizarre picture three days before his death in which neurological phenomena seem to predominate.

The only laboratory data of interest during the second admission were mild glycosuria and mild albuminuria, both of which could go with his mild long-standing diabetes. It is significant that some of his urine specimens were free of albumin. There were changes, however, in the blood count. When this man was readmitted, he had a normal white blood count, hemoglobin, differential count and platelet count.

From the 7th day to the 23rd day, on which he died, two quite remarkable things were seen. There was a tremendous increase in his total white blood count going up to 40,500/mm³, and a drop in his platelets from 170,000 to 52,000/mm³. A variety of immature forms appeared in his peripheral blood including practically all the stem cells in the hematopoietic system. Such a reaction is leukemoid. The distinction between a leukemoid reaction and a leukemia is not

very clear. In fact, sometimes the distinction cannot be made, no matter how carefully the hematologic studies are made. It has been stated, perhaps facetiously, that if the patient dies he had leukemia; if he improves, his reaction was leukemoid.

We have to leave it at this point with a leukemoid-leukemic reaction, with a marked thrombocytopenia and with a hemolytic component.

We have to explain thrombocytopenia and a hemolytic illness, as manifested by reticulocytosis and some drop in hemoglobin and central nervous system lesions. Dr. Eli Moschcowitz in 1925 described for the first time the acute syndrome of acute febrile pleochromic anemia with hyalin thrombi (1). At that time his one case terminated fatally in a short time, and it was believed that most of these cases were of short duration ending fatally without exception.

We now know that the disease sometimes can assume a chronic form. Central nervous system lesions due to micro-angiopathies are characteristic of this disease. The hemolytic phenomena and thrombocytopenia are characteristic and a leukemoid reaction is by no means uncommon in this disease.

Ordinarily this disease is associated with clinical jaundice or at least some increase in bilirubin from hemolysis.

One disturbing factor is that this man had no bleeding tendencies. The disease ordinarily manifests rather significant bleeding tendencies.

One other possibility is that we are dealing with a primary disease of the veins. The patient certainly had an obvious disease of the veins when he came back the second time.

This raises the problem whether this was basically a primary venous disorder of the phlebitis migrans category.

This is a disease of unknown etiology which is characterized by occlusive thrombi in the veins which can either be peripheral, as classic phlebitis migrans, or can involve visceral organs. In phlebitis migrans a significant number had cor pulmonale from infarcts. Perhaps the episode three years ago was a pulmonary infarct and the first manifestation of this phlebitic process.

Terminally, these cases often had a marked thrombocytopenia and severe leukocytosis with immature cells. It was never quite the leukemoid picture that we have here. In the cases of phlebitis migrans proved anatomically, the question of Moschcowitz's disease, disseminated lupus, periarteritis nodosa and the whole group of primary vascular-connective tissue diseases, came up in the differential diagnosis.

If the patient today had thrombotic thrombocytopenia, which Dr. Moschcowitz first delineated, the terminal events probably would be unrelated to the admission three years previously. Thrombosis of the major veins in the Moschcowitz disease is not to be anticipated. If it is a primary phlebitic process, the final and the original diagnoses must be connected.

Without going into any further detail, it seems to me that this man had diabetes mellitus, mild essential hypertension and some degree of generalized atheromatosis, with some coronary artery disease, but I do not think that these caused his death. The disease which was fatal, in my opinion, was either throm-

botic-thrombocytopenia, which would explain his collapse and central nervous system lesions but not explain the involvement of the major venous trunks, or primary disease of the major venous trunks, which would explain his gangrene and much of the hematologic picture.

Dr. Moschcowitz is here and I wonder if he would like to comment.

Dr. Eli Moschcowitz*: I know no more about the disease today than when I first published this.

Dr. Silver: Do you think the terminal events could fit into the picture of Moschcowitz's disease?

Dr. Moschcowitz: No, I never saw phlebitis in the syndrome.

Physician: Do you think there was evidence that he had disease on the arterial side as well as on the venous side of his vascular tree to explain the gangrene, the wrist drop and some of the cerebral manifestations? Why could not this fall into the periarteritis nodosa group?

Dr. Silver: Phlebitis migrans and Moschcowitz's syndrome are close to periarteritis nodosa. This always came up in the differential diagnosis as well as disseminated lupus.

I do not think it is right because massive phlebitis is not part of periarteritis. The gangrene in periarteritis is the result of the occlusion of the smaller blood vessels of the digits particularly, rather than massive gangrene of the extremities. Also, renal lesions are extremely mild here, there is no real febrile course, and significant eosinophilia is missing.

This man has a prolonged prothrombin time. He received Dicumarol, and soon after he needed vitamin K. There are very few lesions which cause prolongation of prothrombin time. These usually are diseases of the hepatic parenchyma. Very little evidence of extensive parenchymal disease of the liver is presented but in diffuse phlebitis very severe involvement of the intrahepatic vessels can be seen, particularly the venous system, with very few signs such as hepatomegaly or decreased hepatic function. There was a little elevation of the serum globulin. He may have had more liver disease than we realize, and that may be related to this prothrombin problem.

Physician: To come back to arterial lesions, apparently something happened quite abruptly when he had trouble with his leg secondarily, and then he had the wrist drop. I was wondering whether you might suggest what vascular lesion on the venous side would give a wrist drop? It would have to be peripheral, and the most common things would be arterial.

Dr. Silver: The wrist drop is more likely neurogenic than arterial. A wrist drop indicates a peripheral neuropathy of some type. It can be part of periarteritis nodosa. You do not have to invoke an arterial lesion for the gangrene.

As I read the protocol, the type of phlegmasia that he had, with bluish discoloration rather than a white leg, is the type of venous disease that can cause gangrene without arterial lesions.

Physician: Could he have had a secondarily infected leg with wet gangrene with neurologic signs on the basis of toxic products?

* Consulting Physician, The Mount Sinai Hospital, New York.

Dr. Silver: From the protocol, this man had a tender cord which was palpable along the right long saphenous vein. He has a big distended extremity full of fluid. The lesion cannot be on the arterial side, at least not exclusively.

Physician: I remember the sequence of events. His phlebitis completely cleared. He was allowed out of bed and was walking around. Therefore, the phlebitis was minimal at that time and the gangrene appeared suddenly.

Dr. Silver: If that happened, then I would anticipate a major arterial occlusion, probably where the popliteal gives off the tibial arteries. If it is clear that the phlebitis with the distended leg was getting better and then the gangrene developed, I would postulate an organic arterial lesion.

Physician: Did you think any of the central nervous system signs could have been due to bleeding?

Dr. Silver: That is possible, except in some of these diseases which we have



FIG. 2. The left ventricle showing multiple mural thrombi in a thinned apical portion.

discussed, diffuse bleeding in the central nervous system is part and parcel of the condition, too. I think they could be explained without invoking atherosclerotic type of bleeding, so to speak.

Dr. Hans Popper:* The discussion should be continued after we have shown you some of the findings.

The lungs presented multiple red wet areas clearly suggesting infarcts. In the pulmonary arteries, many thrombi were found, presumably as a result of a preceding embolization which had become organized. Pulmonary veins were also obstructed by thrombi with organization and recanalization.

The heart was enlarged and weighed over 500 grams. In the pericardium some fibrinous and hemorrhagic fluid was seen. The left ventricle contained a large number of mural thrombi in what was almost an apical aneurysm with significant thinning of the fibrosed myocardium (Fig. 2) with a thickened endocardium, and a coronary occlusion, probably three years old and accounting for the electrocardiographic findings. A few thrombi were also found in the

* Pathologist-in-Chief, The Mount Sinai Hospital, New York.

slightly hypertrophied and somewhat dilated right ventricle and in the left auricle. The myocardium showed multiple myofibrotic foci, and again some thrombotic vessels were seen. The coronary vessels were not very atherosclerotic. The source of all the changes which led to the extensive myofibrosis was an old coronary occlusion, actually many occlusions mainly involving the anterior descending left coronary artery. A few millimeters below its origin, it was occluded by a thrombus. Here we saw some atherosclerotic changes and blood pigment accumulation.

This was not a very complicated case when we first looked at it. There was an old myocardial infarction, probably three years old, some recent mural thrombi on the right side and mural thrombi on the left side, probably with showers of emboli going into many vessels, including the pulmonary arterial branches,

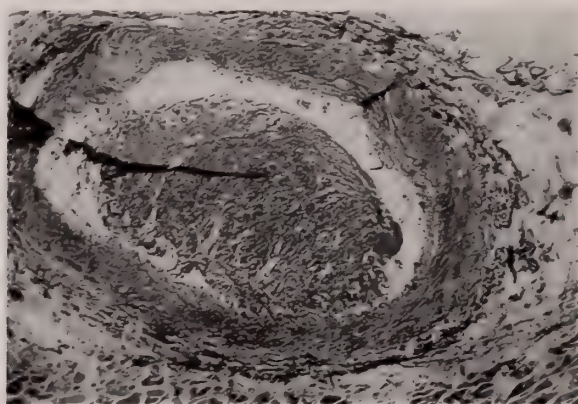


FIG. 3. Small branch of coronary artery occluded by recent fibrin thrombus indicating disease other than simple coronary thrombosis. (Chromotrope aniline blue $\times 63$)

producing pulmonary infarcts. It appeared to be a lesion which we often see in patients who had a little hypertension, diabetes and a myocardial infarct.

The only thing which really spoke against this was the clinical story and, morphologically, the pulmonary vein thrombosis. Maybe this was phlebitis migrans involving the lung, plus a simple myocardial infarct. In the smaller branches of the coronary artery, in the absence of significant arteriosclerosis, fibrin thrombi occluded small coronary arteries (Fig. 3). This does not occur in ordinary coronary occlusion so we had to look further.

Thrombotic lesions were found in large vessels. Dr. Moschowitz has told us that venous occlusion does not belong to the disease he described. To me the vessels involved also were too large to fit the classical picture which usually includes capillaries and arterioles. These were already vessels on the border of visibility but their obstruction probably accounted for the recent myocytolysis and inflammation, and we will understand that old myocardial fibrosis and this recent lesion led to mural thrombi all over. The heart did not show much atherosclerosis.

The artery to the right or gangrenous foot and the arteries on the left

also showed thrombotic occlusions with some disruption of the internal elastic membranes. There was arterial occlusion of the right iliac artery and both iliac veins.

The spleen was very large and weighed 780 grams. We found a recent thrombotic occlusion of what appeared to be the splenic artery. I am not sure whether it was the artery because, on section through the hilum, both the artery and the vein were fairly recently occluded. There must have been first venous and then arterial involvement since the spleen became large. Little splenic subcapsular tissue was intact, and the rest was only a lake of blood (Fig. 4). The patient had arterial infarcts and venous infarcts which produced such a peculiar spleen.

In the intestine, particularly in the colon and rectum, we saw some small ulcers with loss of mucosal lining and again venous as well as arterial throm-

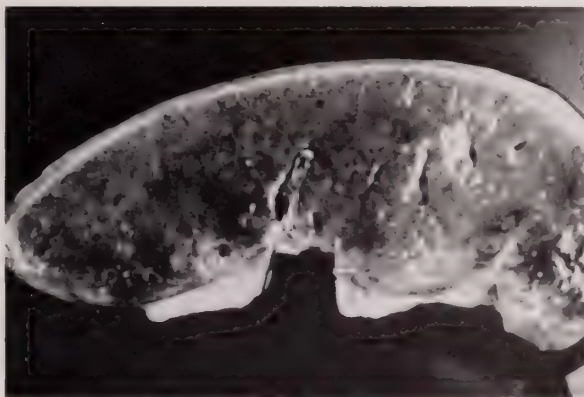


FIG. 4. Spleen with almost complete infarction except for subcapsular rim.

botic emboli. The veins and arteries were occluded. These were vessels which we just barely could see with the naked eye. Such large vessels are not usually involved in Moschcowitz's disease.

In the pancreas, fibrotic areas were found and thrombotic occlusions with changes in the walls of the arteries, resulting in ischemic pancreatic infarcts. Old atherosclerosis with old recanalized thrombi were in the pancreas. Also, we saw small projections into the lumen of smaller vessels. Here for the first time smaller vessels were involved. They were lined by piled up epithelium and showed the classic lesion of Moschcowitz's disease (1, 2). This was thrombotic thrombocytopenia. Some material was deposited in the discontinuous vessel walls. Was this fibrin? We did a fibrin stain which was negative. There was PAS positive polysaccharide projecting into the lumen. This had been described as characteristic for the disease, namely, that the initial lesion of Moschcowitz's disease is a noninflammatory alteration of the arterial wall with deposition of a polysaccharide material and subsequent permeability change and deposition of platelets and fibrin over the area (2, 3).

These were small vessels and small vessels have been emphasized as the seat of the disease since they have no antithrombin material. We have chosen the pancreas as an example but we found these changes in other organs, too. Platelets were deposited after a fibrin thrombus formed, giving rise to typical platelet thrombi.

We apparently had a case of thrombotic thrombocytopenia before us, except that a few things did not fit. Many large vessels were involved, in addition to the small ones. As a matter of fact, there were many more large than small vessels. Secondly, veins were involved. Thirdly, this was originally described as an acute disease but I have seen a case of eight years' duration in which we obtained surgical material showing the lesion (4). The thrombocytopenia in today's case was only two days or three days old at best.

In the classic lesion, microaneurysms form, in which material is deposited

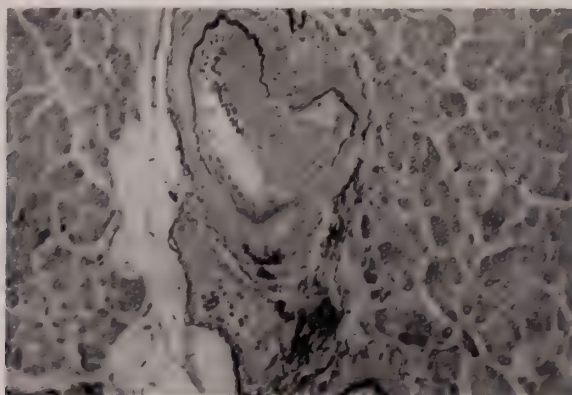


FIG. 5. Aneurysm of pancreatic artery (microangiopathy). (Elastica stain $\times 63$)

(Fig. 5). This finding was another support that we were dealing with Moschcowitz's disease.

We found old pancreatic involvement with fibrosis. Others have reported long survival (5) and I saw two cases in Chicago of old lesions, one of eight years and one of three years, with predominant endocrine involvement and diabetes as in this instance. The diabetes may be here of late maturity onset and not spontaneous diabetes but actually a pancreatic diabetes from Moschcowitz's disease.

In the cellular bone marrow, red cells and red cell precursors predominated with a large number of megakaryocytes. There was probably an overproduction of platelets with loss by the formation of thrombi supported here. The diagnosis has been made in some instances from the marrow (6).

Many other organs were involved. For instance, we saw multiple thrombotic thrombocytopenic lesions in the peripheral muscle and in the adrenals. There was small arterial submucosal involvement in the stomach.

In the kidney many infarcts were present again with larger as well as smaller vessel involvement. Some of the arterial involvement was old with recanalization (Fig. 6). Some veins were involved and recent more segmental lesions were

seen. The glomeruli were normal. However, something had been happening in the kidney because we found features of a lower nephron type of nephrosis with focal necrosis and accumulation of immature cells from the blood stream. This is usually evidence of shock.

There was an undiscovered small carcinoma of the prostate and periphlebitic

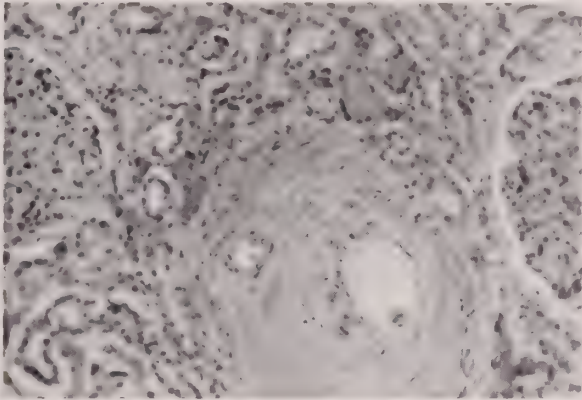


FIG. 6. Recanalization of branch of renal artery previously occluded by thrombus. (H & E $\times 63$)

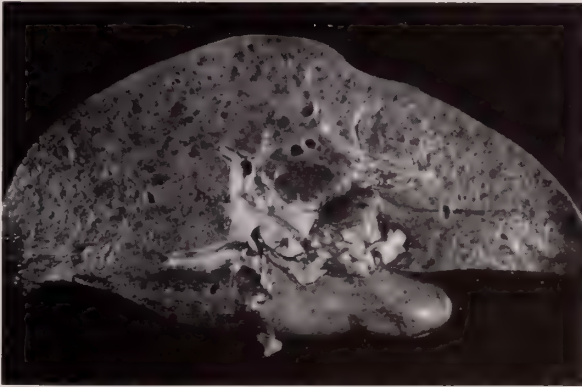


Fig. 7. Nodular appearance of the cut surface of the liver.

inflammation around organized thrombosis of the prostatic veins which occurs under many conditions. In the testes we saw small fibrotic foci which resulted from old vascular lesions.

The lymph nodes were large. We have diagnosed Mosecowitz's disease from lymph nodes in the past but here we found only lipid deposits.

The liver was very large and weighed 2,200 grams. Grossly, irregular nodules of different sizes were seen as in postnecrotic cirrhosis (Fig. 7). Hepatic arterial thrombosis was present and this disease involved large arteries of the liver (Fig. 8). In the nodules preservation of the architecture was noted as well as

differential regeneration with some fatty metamorphosis. Some of the lesions of the large arteries were organized and were not of three days' duration but months and even years old. Some were recent with beginning thrombosis. Interruption of the wall with beginning aneurysm formation in a segmental fashion was seen. This was typical involvement of Moschcowitz's disease. However, the

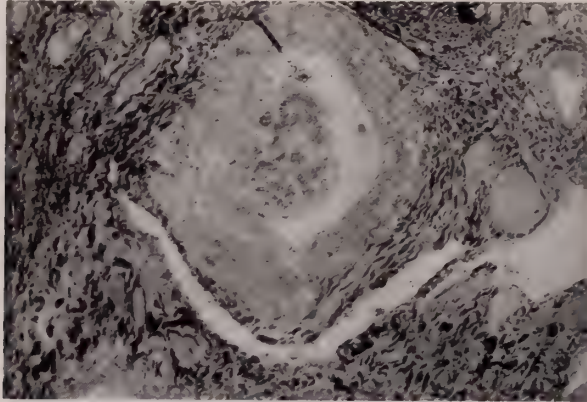


FIG. 8. Organizing platelet thrombus in branch of hepatic artery. (Chromotrope aniline blue $\times 63$)

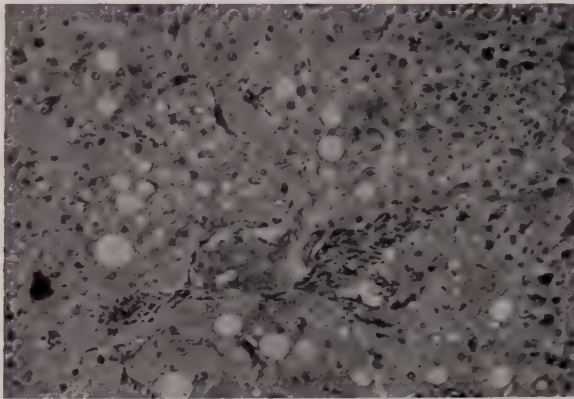


FIG. 9. Fibrin thrombus in hepatic vein branch. (Chomotrope aniline blue $\times 120$)

portal vein branches were also involved and contained organized thrombi (Fig. 9). The small vessels of the peribiliary plexus were filled with fibrin as were neighboring small hepatic arterial branches. The central veins of the lobule often were involved in this type of lesion. Many areas in the liver showed ischemic necrosis. In the portal tracts reaction with giant cells about fat was seen. This meant that necrotic hepatic tissue had been brought to the portal tract and created lipogranulomas. I presume that the entire peculiar type of cirrhosis which was found was probably a postnecrotic cirrhosis on a vascular basis. I have never seen this type of cirrhosis before. I assume that here repeated

arterial and venous obstruction led to gradual transformation into a cirrhotic liver.

Tremendous reticuloendothelial hyperplasia, as a reflection of the leukemoid reaction, and a large amount of iron in the reticuloendothelial cells, as a result of hemolysis, were also found in the liver.

I think we have to call this disease generalized chronic thrombo-embolism. There was involvement of the coronary arteries with multiple infarcts and cardiac failure. Pulmonary infarcts were clinically not apparent, except for rales. Renal infarcts produced hematuria. Hepatic infarcts led to cirrhosis and to the coagulation defect. A massive splenic infarct developed and this acute infarction of the spleen may have led to leukocytosis and the leukemoid reaction. A pancreatic lesion was present with fibrosis and clinical diabetes. Iliac artery involvement produced gangrene. Lesions were also in the testes, rectum, skeletal muscles, stomach, adrenals and probably the central nervous system. Veins which have been spared in previous cases (7) were also involved in the spleen, lungs, prostate and liver (both portal and hepatic), and bilateral thrombophlebitis developed in the legs.

What was the etiology? It was too widespread to be arteriosclerotic emboli and there was venous involvement. It could not be from the mural thrombi in the heart because of the venous involvement and phlebitis migrans is unlikely because of arterial involvement.

I think we are dealing with a lesion which probably has not been described before. It is a large vessel variety of thrombotic thrombocytopenia of Moschcowitz. We found the platelet thrombi, the subintimal, nonfibrinous deposits, the segmental distribution, and the thrombocytopenia with many megakaryocytes and the nervous system involvement.

What does not fit? The capillaries are free and veins were involved. The patient was a male and less than $\frac{1}{3}$ of the cases were males (8). The disease was of very long duration. The venous involvement was possibly secondary to large arterial involvement. The very peculiar postnecrotic cirrhosis I think, was ischemic cirrhosis from lipogranulomas and fibrin thrombi in the portal tract.

In conclusion, I believe it was a variant of thrombotic thrombocytopenia or Moschcowitz's disease.

Dr. Silver: I was disturbed in trying to make a diagnosis of thrombotic thrombocytopenia purpura because of the venous involvement. Apparently it disturbed Dr. Popper too, and if it is a new manifestation of the disease, I think then that we are present at the birth of a modification of the syndrome.

In the more recent descriptions of the peculiar subendothelial material that accumulates in this microangiopathic type of aneurysmal lesion, difficulties were encountered in identifying this as fibrin, particularly when immunologic methods are used since an immunological response to fibrin does not occur unless it is bound to serum albumin. Although it may really be fibrin, one may not be able to demonstrate that.

Up to 1955 I was able to find some eighty reported cases of Moschcowitz's disease. It is true that females predominate, but there are enough males so that

this should not disturb us at all. Reticulocytosis is characteristic of the disease. The leukemoid reaction is extremely frequent, so that we at least were led in that direction. There are several case reports lasting as long as six years, as Dr. Popper indicated, and I think he mentioned even eight years, so that the relatively chronic course should not delude us.

It was an extremely interesting and puzzling case. We were able to put lesions on the arterial and the venous side. We had difficulty in explaining it. Apparently we still have some difficulty in explaining it unless it represents a subgroup of this very bizarre and interesting syndrome.

*Dr. Howard Moscovitz**: I took care of this patient during his illness. The diagnosis did suggest itself when the bizarre neurological findings developed. Up until that point we were completely confused by this coincidence of venous and arterial obstruction which resulted in gangrene in both extremities.

Final diagnosis:

ATYPICAL THROMBOTIC THROMBOCYTOPENIA (MOSCHCOWITZ'S DISEASE) WITH INVOLVEMENT OF LARGER VEINS AND ARTERIES.

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* Assistant Attending Physician, The Mount Sinai Hospital, New York.

Radiological Notes

BERNARD S. WOLF, M.D., EDITOR

New York, N. Y.

LESTER R. CAHN, D.D.S., Sc.D., LEON EISENBUD, B.S., D.D.S.,
JACK KLAPELL, B.S., D.D.S., AND MELVIN BLAKE, B.S., D.D.S.

CASE NO. 162

A 52 year old male complained to his dentist of pain and tenderness in the upper right cuspid tooth. X-ray examination showed an area of rarefaction around the apex of the tooth extending to the alveolar margin (Fig. 1). This area was eccentrically placed. The root of the tooth appeared to be relatively intact but the lamina dura about the root was missing medially. The periphery of the lucent area was scalloped and irregular without any evidence of reactive bone formation. The original impression was that a periapical osteitis existed. The tooth was extracted and the area curetted. The curettings were not examined histologically. A dental bridge was made to replace the removed teeth. After several months, however, the patient returned again complaining of discomfort in the same area. Additional teeth were removed and the area was again curetted. After this, however, the local condition deteriorated rapidly with marked bulging of the palate and adjacent buccal area. Re-examination of the area showed obvious progression in the area of bone destruction with an irregular air-filled cavity within the soft tissue defect (Fig. 2). The moth-eaten appearance of the eroded periphery at this time was characteristic of neoplastic invasion.

Biopsy of the mass showed an epidermoid carcinoma and further investigation indicated that the origin was in the adjacent maxillary sinus.

Carcinoma of the maxillary sinus occasionally will grow predominantly inferiorly. As a result, the first manifestation may be pain in or adjacent to one or another tooth. The case presented demonstrates such a sequence of events and emphasizes the importance of histologic examination of any abnormal tissue found after tooth extraction.

Case Report: CARCINOMA OF THE ANTRUM PRESENTING AS A PERIAPICAL OSTEITIS.

CASE NO. 163

A lesion of the mandible in a 16 year old girl was found by the dentist on routine oral roentgenograms. All the teeth were vital. The mandible showed a large lucent ovoid zone in the horizontal ramus of the mandible below the bicuspid and first molar teeth (Fig 1). The upper margin of the lesion extended

*From the Division of Oral Pathology, the Department of Pathology, The Mount Sinai Hospital, New York, N. Y.

upwards between the teeth. The apices of the roots of the adjacent teeth were flattened but not destroyed. The periphery of the lesion showed no reactive bone formation, and no sclerotic margin. The trabecular structure of the adjacent bone was intact. There was a suggestion of slight bulging inferiorly of the residual normal bone along the lower margin of the ramus. There was no evidence of any periosteal reaction.

Intraoral exploration was recommended. On opening the cavity, only sero-sanguinous fluid was found. There was no evidence of any lining membrane or embryonic tooth remnant. The diagnosis was a "traumatic bone cyst."



Fig. 1.

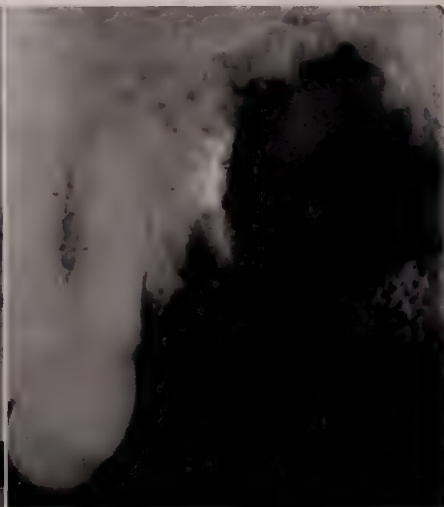


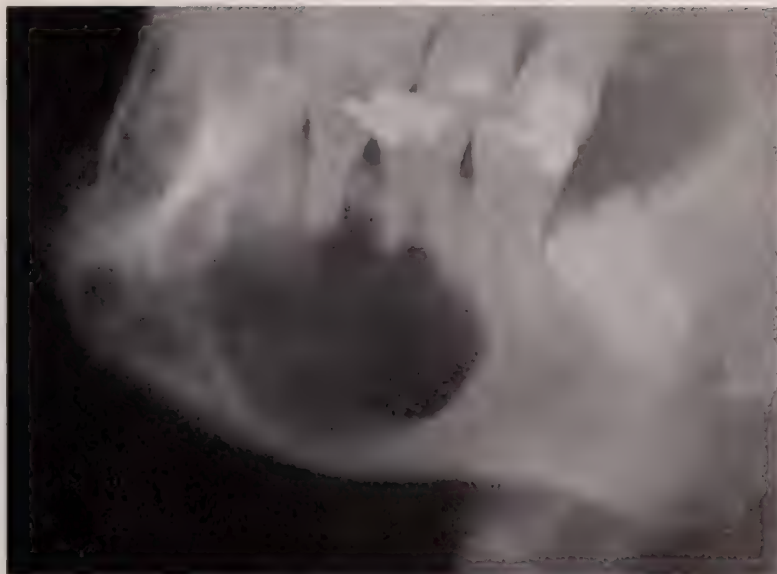
Fig. 2.

Case 162, Fig. 1. A discrete but poorly and irregularly demarcated lucent area is present adjacent to the root of the upper right cuspid tooth. The lesion is eccentric and extends to the alveolar margin. Most of the lamina dura about the root is destroyed. There is no reactive bone formation. The root of the tooth appears to be intact.

Case 162, Fig. 2. Re-examination several months later shows progress of the destructive process with an irregular moth-eaten periphery. In the center of the soft tissue occupying the defect, there is a funnel-shaped more lucent zone which represents air trapped in the necrotic center of the tumor.

The exact etiology of a bone cyst of this character is unknown, but apparently a variable sized cavity is produced as a result of trauma and resulting intramedullary bleeding. The hematoma, originally expansive, clots and becomes necrotic. It is most common in younger individuals and occurs more frequently in the lower than in the upper jaw. Important diagnostic features are that the associated teeth are vital, the cyst-like cavity is not associated with the teeth but skirts around the roots usually indenting between them and there is no peripheral sclerotic rim as usually seen around an epithelial-lined or odontogenic cyst.

Case Report: TRAUMATIC BONE CYST OF THE MANDIBLE.



Case 163, Fig. 1. X-ray examination of the mandible shows an ovoid discrete markedly lucent area in the horizontal ramus of the mandible related to the bicuspid teeth and the first molar. The roots of these teeth are flattened. The lucent area extends upward between the roots. There is no evidence of any trabeculation within the bone defect or of any sclerotic peripheral bone margin. The lower margin of the ramus bulges slightly inferiorly at the site of the lesion.

CASE NO. 164

A 54 year old woman was found to have a most peculiar trabecular pattern in the mandible during a routine dental x-ray examination (Fig. 1). The number of trabeculae appeared to be increased but much more striking was the remarkable horizontal position of the individually thickened trabeculae replacing the normal interlacing pattern. The impression gained was that the trabeculae surrounding the roots of the teeth were compressed or displaced by the occlusal forces indicating that the bone must be unusually soft. In places, the individual trabeculae were closer together and not sharply demarcated, producing a "groundglass" appearance, such as is seen in a variety of conditions including hyperparathyroidism and polyostotic fibrous dysplasia as well as in Paget's disease. However, the bizarre horizontal position of the trabeculae in this patient and the fact that individual trabeculae can be discerned is very characteristic of Paget's disease. Additional findings in dental x-rays in cases of Paget's disease include radiolucent areas within the bone representing the earliest hypervascular phase (Fig. 2). These rather discrete lucent areas are frequently located adjacent to the roots of the teeth and may easily be mistaken for an apical "abscess." However, in Paget's disease the teeth are usually vital and pain may be a prominent feature. In addition, hypercementosis or an excessive deposit of

cementum on the roots of the teeth producing a remarkable increase in density is often found in Paget's disease. While hypercementosis may occur in other conditions, if it is marked and diffuse, Paget's disease should be considered as a possibility.

Case Report: PAGET'S DISEASE OF THE MANDIBLE WITH CHARACTERISTIC CHANGES.

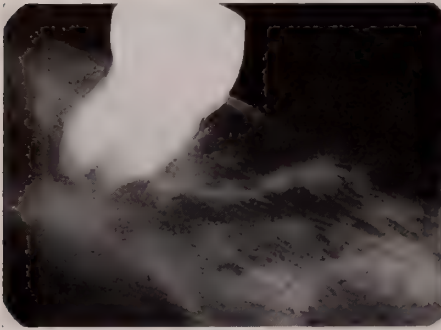


Fig. 1.

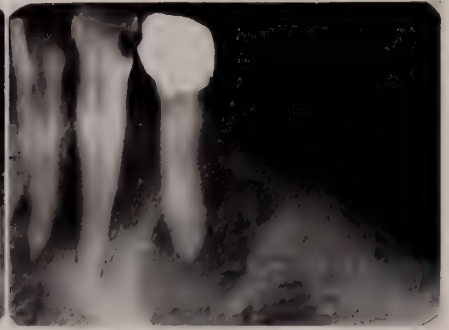


Fig. 2.

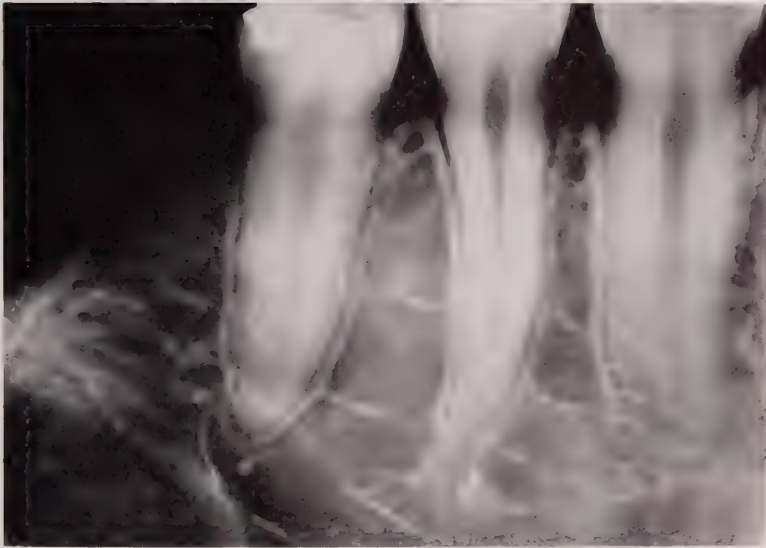
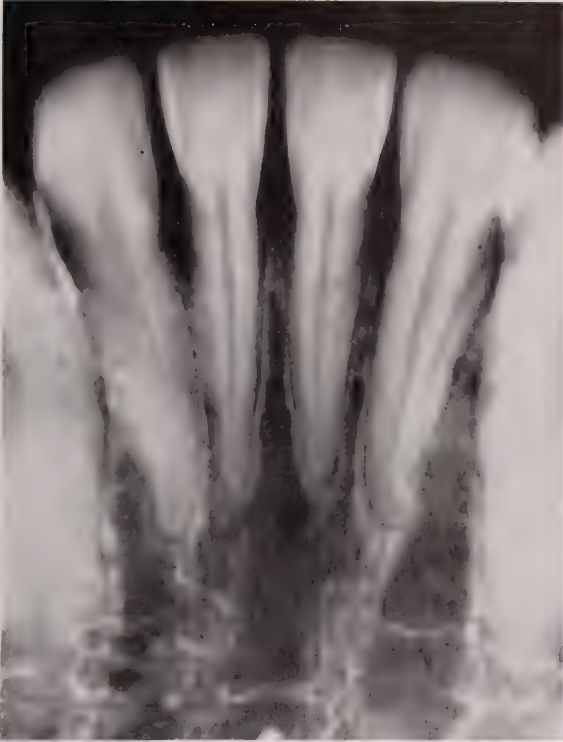
Case 164, Fig. 1. The trabecular structure of the mandible shows a remarkable transformation from the normal interlacing pattern to horizontal or transverse thickened trabeculae which can be individually identified in most places. Around the root of the tooth, there appears to be a somewhat arcuate group of trabeculae suggesting extrinsic pressure due to the force of occlusion. The roots are unusually dense.

Case 164, Fig. 2. A fairly well-demarcated lucent zone is seen around the apex of the tooth, the resorptive or hypervascular phase of Paget's disease. This appearance can be mistaken for a periapical "abscess" if the more characteristic increase in density and abnormal course of trabeculae cannot be recognized in adjacent areas.

CASE NO. 165

A Negro male of about 22 years of age appeared at the dental clinic for a prosthesis. On routine x-ray examination of the teeth, however, an extraordinary diffuse change in the fine bony structure of both the mandible and the maxilla was found. The intertrabecular spaces were hugely widened resulting in a marked diminution in the number of trabeculae seen. In places, the residual trabeculae were thin while in other areas they were thick and transverse. Because of these changes, the possibility that the patient was suffering from a disease of the hematopoietic system was suggested. Hematological examination demonstrated the presence of sickle cell anemia. It should be pointed out, however, that a specific diagnosis of sickle cell anemia cannot be made roentgenologically since similar changes may be seen in other conditions, specifically Cooley's anemia (Thalassemia) and Gaucher's disease.

Case Report: SICKLE CELL ANEMIA DISCOVERED BY ROENTGEN EXAMINATION OF THE TEETH.

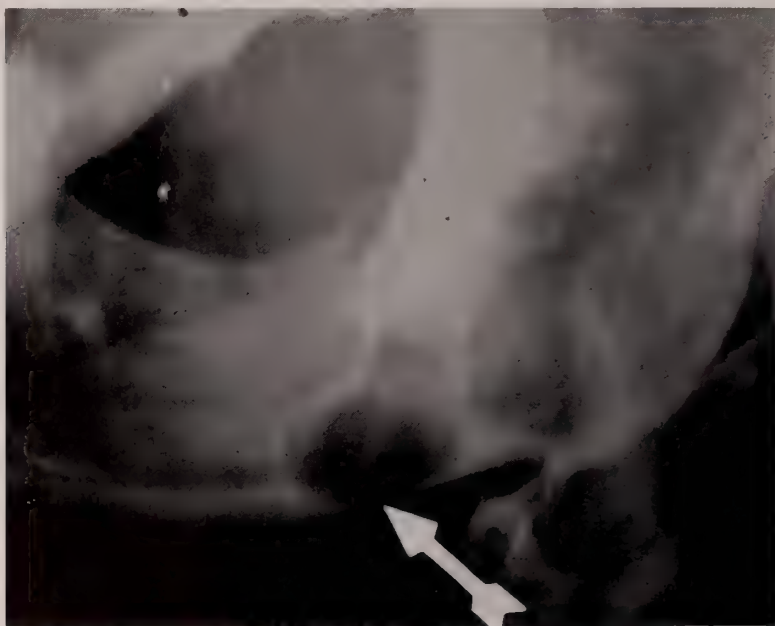


Case 165, Fig. 1A (Top). The medullary spaces between the trabeculae are markedly widened. Individual trabeculae are thick with loss of the normal interlacing pattern. The lamina dura and teeth are unaffected.

Case 165, Fig. 1B (Bottom). Similar, more marked changes, are present elsewhere indicating diffuse involvement of all the cancellous bone.

CASE NO. 166

A lesion of the horizontal ramus of the mandible was found on routine oral roentgen examination of a 52 year old male. In the inferior and posterior portion of the horizontal ramus of the mandible, an ovoid, sharply demarcated, homogeneous, lucent zone with sclerotic rim was present. This peripheral ring or rim was quite thick. The lesion extended into the cortical bone of the inferior margin of the mandible in front of the angle. There was no evidence of any residual tooth structure or of periosteal new bone formation. Exploration was recommended.



Case 166, Fig. 1. A sharply demarcated, homogeneous, lucent, ovoid area is present (arrow) adjacent to the inferior margin of the mandible anterior to the angle. A thick sclerotic border is present. Bone resorption extends into the cortex inferiorly but there is no evidence of pathological fracture or periosteal reaction. No residual tooth structures are present.

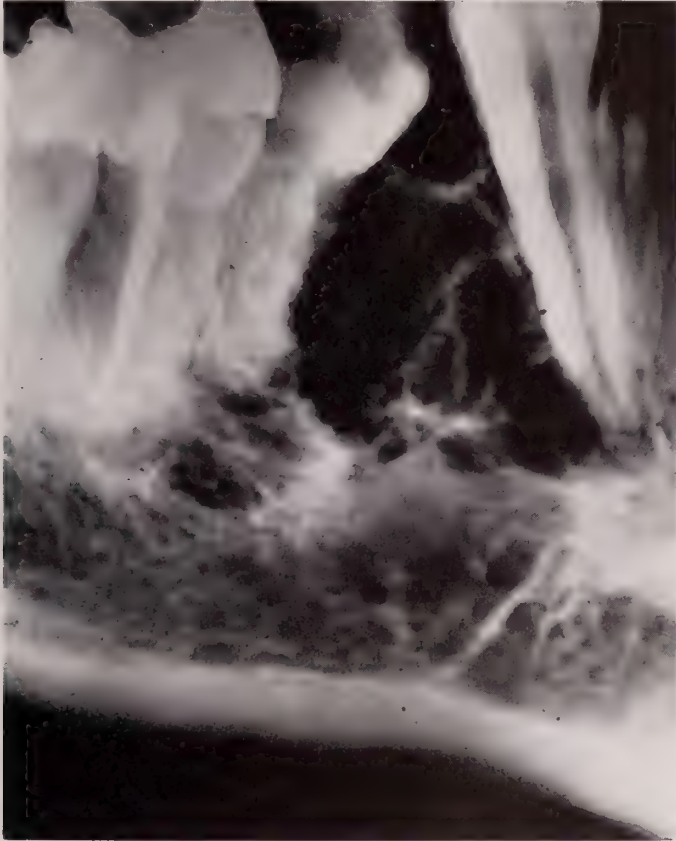
Operative intervention demonstrated that the lesion was solid and contained salivary gland tissue. This condition is now rather well known and has been designated as "idiopathic bone cavities in the mandible." At operation, the typical finding is a defect in the lingual plate and the presence of soft tissue in a cavity within the bone contiguous and continuous with sublingual structures. The tissue in the bone defect is sublingual salivary gland tissue that has been enclaved in the bone during embryological development. Not infrequently, the lesions are bilateral. The position of the lesion in the posterior inferior margin of the mandible is quite typical. The rather markedly sclerotic border usually more prominent than that seen with a residual or primordial epithelial-lined cyst, is

also characteristic. An incorrect diagnosis of dentigerous cyst may be made in such instances when unerupted molar teeth happen to be present. If the true nature of this lesion were known, operative intervention would not be necessary.

Case Report: SALIVARY GLAND INCLUSION IN THE MANDIBLE.

CASE NO. 167

On routine dental examination of a 19 year old girl, a peculiar abnormality was noted in the alveolar margin of the mandible (Fig. 1). The lesion is rather



Case 167, Fig. 1. At the upper border or alveolar margin of the mandible, an expanding, poorly demarcated, multilocular lesion is present. The trabeculae within the lesion are coarse but appear to maintain a cancellous structure. The adjacent teeth are spread apart.

poorly demarcated and has a coarsely trabeculated or multilocular appearance. The adjacent teeth are displaced laterally by this lesion indicating its expanding character. The appearance was rather typical for a small ameloblastoma. However, a somewhat similar appearance may be seen in giant-cell reparative granuloma, myxoma and hemangioma. It is of considerable importance, however, to make the diagnosis of ameloblastoma at an early stage since a conservative

operation at this time may be feasible and curative. In the late stages, cure without radical resection is ordinarily not possible.

Case Report: SMALL AMELOBLASTOMA—AN INCIDENTAL FINDING.

CASE NO. 168

A 40 year old male complained of moderate discomfort in the lower right cuspid area. Roentgenograms of the teeth (Fig. 1) showed a poorly defined lamina dura about the root of the cuspid with a suggestion of minimal bone resorption on each side of the root. It was thought that these changes were the result of undue pressure by a prosthesis that the patient had been wearing for several years. He was advised to remove the denture but his symptoms did not improve. Re-examination two weeks later showed rapid increase in the

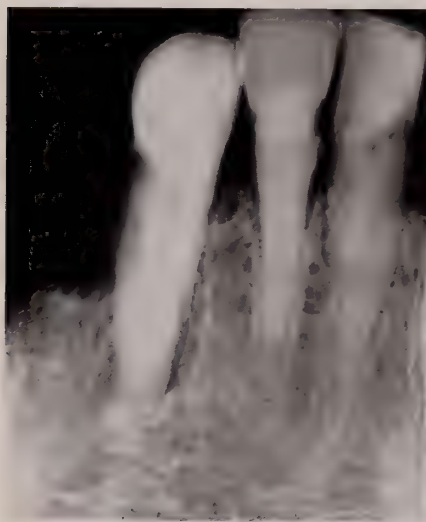


Fig. 1.



Fig. 2.

Case 168, Fig. 1. Film of the right lower cuspid area shows some resorption of the lamina dura and some irregularity in the trabecular structure adjacent to the root.

Case 168, Fig. 2. Re-examination two weeks later shows marked increase in bone destruction on each side of the root of the cuspid tooth. This area is poorly demarcated with a ragged periphery (arrow).

resorption of bone surrounding the apex of the tooth (Fig. 2). The involved area was poorly demarcated with no bone reaction. The tooth was removed and the area curetted for biopsy. Histological examination showed "fragments of carcinoma resembling a bronchogenic carcinoma." A roentgenogram of the chest was then done and showed a discrete lesion in the right lung which, on further investigation, was demonstrated to be a bronchogenic carcinoma. The patient went downhill rapidly and died shortly thereafter.

Case Report: BRONCHOGENIC CARCINOMA FIRST EVIDENT AS A METASTASIS ADJACENT TO A TOOTH.

Abstracts

Papers Presented before the Research Club of The Mount Sinai Hospital New York, N. Y.

Identification and Partial Purification of a Post-Lipomul Lipase in Plasma of Dogs. Jacques I. Kessler, M.D.

Administration of heparin to lipemic subjects has been shown to result in elevation of plasma free fatty acids (FFA), and in acceleration of the anodic electrophoretic mobility of serum lipoproteins.

These effects are attributed to an enzyme—lipoprotein lipase (LPL) or "clearing factor" which is released by heparin into the circulation. This enzyme catalyzes the hydrolysis of the triglyceride component of chylomicrons and other low density lipoproteins thus liberating FFA *in vitro* at a rate temporarily exceeding the ability of the organism to remove them.

At these high levels a significant fraction of FFA become associated with serum lipoproteins thereby increasing their negative electrostatic charge. These FFA-rich lipoproteins exhibit an increased anodic electrophoretic mobility, alpha-lipoproteins appear in the pre-albumin region and beta-lipoproteins move in the region between alpha- and beta-globulin.

Elevation of plasma FFA and electrophoretic changes similar to those reported after injection of heparin to lipemic subjects have been described after intravenous administration of Lipomul.

It was assumed that infusion of Lipomul results in release of a lipolytic enzyme, similar or identical with the postheparin LPL, by a mechanism independent of exogenous heparin.

To test this possibility Lipomul was infused into five mongrel dogs and blood samples were withdrawn at varied intervals of time. The lipolytic activity of post-Lipomul plasma was determined by its ability to release FFA from an "activated" triglyceride substrate. Maximal activity was determined in the samples drawn at completion of the Lipomul infusion. The mean activity was sufficient for liberation of $4.86 \pm 0.56 \mu\text{Eq}$ FFA by one ml of plasma during one hour of incubation. This activity could account for lipolysis of only a small fraction of the Lipomul triglycerides actually removed from the plasma. This indicates that particulate triglyceride is cleared from the circulation mainly by a mechanism independent of intravascular lipolysis.

The properties of the post-Lipomul lipase resembled those of the postheparin LPL. 1M NaCl and protamine sulfate, which are inhibitors of LPL, also inhibited the activity of post-Lipomul lipase. NaF which inhibits the activity of pancreatic lipase had little or no effect on post-Lipomul lipase.

Post-Lipomul lipase was partially purified by using the method of $\text{Ca}_3(\text{PO}_4)_2$ gel adsorption and subsequent elution with sodium citrate. Incubation of purified post-Lipomul lipase in the presence of lipemic plasma resulted in release of FFA and in acceleration of the anodic electrophoretic mobility of lipoproteins. These changes were similar to those produced by postheparin LPL.

In these respects post-Lipomul lipase is similar to, but not necessarily identical with postheparin LPL.

It was concluded that in the presence of high plasma levels of particulate triglyceride, a tissue lipase, possibly lipoprotein lipase, can be released into the circulation. The mechanism of release is not related to exogenous heparin.

Familial Hypohaptoglobinemia Associated with Erythrocytic Glucose-6-Phosphate Dehydrogenase Deficiency. Arlan Gottlieb, M.D., Nathaniel Wisch, M.D., and John Ross, PhD.

While studying a patient with Hodgkin's disease a deficiency of erythrocytic glucose-6-phosphate dehydrogenase was discovered. Subsequent study of the patient's family revealed a familial deficiency of this enzyme as well as an independent inheritance of hypohaptoglobinemia.

Erythrocytic glucose-6-phosphate dehydrogenase was determined by the technique used by Zinkham *et al.* Serum haptoglobin determinations were performed in a family group of 19 members by the technique of Connell and Smithies. Haptoglobin typing was done after starch gel electrophoresis in borate buffer at a pH 8.8 according to the method of Smithies and in phosphate buffer at pH 7.0 as described by Laurell. Blood typing was obtained on all family members in order to confirm legitimacy. Complete hemograms were also done. Except for the one member of the F-1 generation all the family members studied were in good health and without evidence of hemolysis.

In the F-1 generation a 2-2 haptoglobin pattern was associated with elevated haptoglobin levels. In the F-2 offspring there were five 2-1 patterns and three 2-2 patterns. Two of the patients who subsequently proved to have 2-2 patterns had no measurable haptoglobin by peroxidase activity. The F-3 generation revealed seven 2-1 and three 2-2 phenotypes. Hypohaptoglobinemia was found in five cases with a 2-1 pattern and four individuals with a 2-2 pattern. Normal haptoglobin levels were likewise associated with both 2-1 and 2-2 phenotypes.

The results of this study as regarding a tri-allelic inheritance of haptoglobins are discussed.

The coincident finding of erythrocyte glucose-6-phosphate dehydrogenase deficiency in five family members bore no relation to the inheritance of haptoglobins.

The Effect of Acetazolamide on Secretion of Sodium and Potassium in the Human Stomach. Arthur E. Lindner, M.D., Nathaniel Cohen, M.D., David A. Dreiling, M. D., and Henry D. Janowitz, M.D.

The effect of intravenous infusion of the carbonic anhydrase inhibitor acetazolamide on the electrolyte composition of basal and histamine-stimulated gastric secretion has been studied in twenty human subjects, employing a drug dosage of 50 to 100 mg/Kg.

Acetazolamide causes a decrease in output of hydrogen, chloride, sodium and potassium ions and a decrease in volume rate of secretion. These effects are

demonstrated in the spontaneously secreting stomach but are more marked in the stomach stimulated by histamine. Reduction in potassium and chloride output correlates directly with reduction in volume rate; decrease in hydrogen output, however, is greater than can be accounted for by flow rates and decrease in sodium is less. The familiar inverse relationship between concentrations of sodium and hydrogen ions, present in both basal and histamine-stimulated secretion, persists after acetazolamide infusion.

The behavior of sodium ions is consistent with the theory that at least part of the sodium in gastric juice is derived from exchange for hydrogen. Acetazolamide does not interfere with this mechanism.

The behavior of potassium ions suggests that part of the potassium of gastric juice is derived from acid secreting cells; yet the presence of potassium in anacid specimens indicates that some potassium is also secreted without hydrogen ions. These findings are in agreement with the theory of a dual source of potassium, from both parietal and nonparietal secretion.

Effects of acetazolamide on the secretion of sodium and potassium are believed to be secondary to changes induced by the compound on primary mechanisms of acid secretion.

Angiotensin II-I¹³¹ Degradation In Vitro with Normotensive and Hypertensive Human Sera. Robert Wolf, M.D., Milton Mendlowitz, M.D., Julia Pick, B.S., Gitlow, S. E., and Nostrat E. Naftehi, M.S.

The effect of normotensive, untreated and treated primary benign hypertensive and untreated secondary renal hypertensive human sera on the degradation of angiotensin II *in vitro* has been investigated using iodine-131 labeled angiotensin II. The technique depends on the ability of human sera to degrade angiotensin II-I¹³¹ and the quantitative determination of the radioactive degradation-product (iodine-131) by means of paper radiochromato-electrophoresis.

The results of these experiments indicate that untreated primary benign hypertensive sera enhances the degradation of angiotensin II-I¹³¹ *in vitro*. This may be due to the presence of one or more unique factors which are present in the sera of these patients or to the increased concentration or biologic activity of a factor (angiotensinase) normally present in human sera. The observation that heat inactivation of serum, whether from a normotensive or untreated primary benign hypertensive subject, increases the amount of angiotensin II-I¹³¹ degraded suggests that an inhibitor may be present in human serum which restrains the action of this factor (or factors) and that this inhibitor is destroyed by heating to 57° C for 30 minutes.

The reduction in the percent angiotensin II-I¹³¹ degraded in the treated primary benign hypertensive patients whose blood pressures were normal or almost normal implies that the factor (or factors) which enhances the degradation of angiotensin II-I¹³¹ is decreased or altered by the antihypertensive treatment. The greater *in vitro* degradation of angiotensin II-I¹³¹ by untreated primary benign hypertensive sera than by normotensive sera is in contrast to the

slower turnover *in vitro* of angiotensin II-I¹³¹ and implies that factors are present in the hypertensive patient which result in a slow *in vivo* turnover rate despite a relatively great *in vitro* degradation.

The normal values for the percent angiotensin II-I¹³¹ degraded in the two patients with secondary renal hypertension is in contrast to the results obtained in the untreated primary benign hypertensive group. It may be feasible to employ this procedure to distinguish patients with secondary renal hypertension from those with primary hypertension.

THE THALASSEMIAS: VARIANTS AND ROENTGEN
BONE CHANGES

JOHN E. MOSELEY, M.D.

New York, N. Y.

Thalassemia is a hereditary disorder of hemoglobin synthesis which is far more prevalent than was formerly believed. The disease has been found with high frequency in the Central and Eastern Mediterranean regions and in parts of North Africa. The incidence is particularly high in Italy, Greece and adjacent geographical areas. A surprisingly high incidence, however, is now being uncovered in a broad belt extending through the Middle East and India to South-east Asia. The condition has also been reported in American Indians and Negroes and is now recognized to be a common disorder of extensive distribution.

Advances in our knowledge of the hemoglobinopathies and thalassemia are continuing at such a rapid pace that much of what is written about them today must be considered tentative. It is generally agreed that the spectrum of disorders included under the designation thalassemia are a heterogeneous group of inherited abnormalities with similar hematologic and clinical features. There are several classifications of the thalassemias. Some of these are based on the most recent developments in our knowledge of the hemoglobins. The introduction of starch block electrophoresis, for instance, has resulted in the discovery that the minor A_2 fraction of hemoglobin is present in excess of three per cent in most patients heterozygous for thalassemia. This finding, in addition to the fact that microcytosis and decreased osmotic fragility (microcythemia) are characteristically found in the heterozygote, has resulted in a classification based on these features. Thus, there is: 1) a "classical" thalassemia in which A_2 is present in excess of three per cent in association with microcythemia; 2) a thalassemia in which there is an elevated A_2 but without microcythemia and, 3) thalassemia with microcythemia but without an excess of A_2 . The homozygous state of "classical" thalassemia is thalassemia major and both other types may interact with "classical" thalassemia to produce the major form of the disorder.

The hemoglobin molecule has been partly reconstructed and appears to contain nineteen different amino acids. The entire molecule is composed of approximately 560 amino acid residues. The amino acids are united to form polypeptides and each molecule has four polypeptide chains arranged as two pairs. These have been designated respectively as the α chains and β chains. It is considered at present that the thalassemia mutant genes lead to amino acid substitutions which affect the rate of hemoglobin synthesis. Accordingly, the thalassemias are classified as α thalassemia or β thalassemia depending on whether the α or β chain production of hemoglobin A is decreased.

Clinical classifications of the thalassemias have not met with universal ac-

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

ceptance because of the lack of more distinctive characteristics than the classic clinical and hematological features. Although the introduction of starch block electrophoresis for the determination of hemoglobin A₂ and techniques for the quantitative estimation of fetal hemoglobin have added significantly to the diagnostic criteria, there is still need for a more objective basis for diagnosis. In thalassemia, unlike the hemoglobinopathies, a specific alteration of the hemoglobin molecule has not been demonstrated. Ingram and Stretton (1), however, have suggested recently that the thalassemias may be due to amino acid substitutions similar to those of the hemoglobinopathies but in which the substitution, although altering the rate of hemoglobin synthesis, does not result in a difference in the net charge of the protein and therefore does not alter the normal electrophoretic rate.

Clinically, thalassemia may occur in two main forms. These are: 1) thalassemia minor, which occurs in individuals who are heterozygous for the autosomal dominant trait *i.e.*, it is inherited from one parent only and 2) thalassemia major, which occurs in individuals who are homozygous for the condition *i.e.*, it is inherited from both parents.

Thalassemia minor varies considerably in its grades of severity and ranges from a barely perceptible erythrocytic anomaly to forms in which there are moderate anemia, icterus and splenomegaly (2). When the condition is asymptomatic and without anemia it may be referred to as *thalassemia minima* or the *trait*. Another form of thalassemia minor is *Rietti-Greppi-Micheli disease*. In these patients there is a moderate anemia. The erythrocytes show a microcytosis and hypochromia. Oval and target cells are characteristic and the osmotic fragility is reduced as it is in all forms of thalassemia. There is generally a slight to moderate splenomegaly. Fetal hemoglobin is sometimes increased and A₂ hemoglobin is regularly increased (3). The most severe forms of thalassemia minor fall into a hazy group designated *thalassemia intermedia*. This term is clinically useful but not well defined. It covers a clinical area where the more severe thalassemia minors merge with the less severe thalassemia majors and is further obscured by syndromes due to double heterozygosity for thalassemia and various abnormal hemoglobins.

Thalassemia major (Mediterranean disease, Cooley's anemia, erythroblastic anemia) is usually a severe disorder of infants and children few of whom survive beyond adolescence. It is commonly considered that most patients succumb before puberty but as Smith (4) has pointed out, it is difficult to estimate the precise period of puberty in these patients since the development of sexual maturity is considerably retarded. The disease is not always so grave, however, and cases extending into late adolescence and adulthood are now being described. *Both the homozygous and heterozygous states, therefore, show considerable variation in their degrees of severity.*

Classical thalassemia major usually becomes evident within the first year or two of life, more frequently in the latter half of the first year. The patients are severely anemic and present a characteristic facial appearance which tends to make them resemble each other more than they resemble other members of their own family. The head is large and there is usually some prominence of the

frontal and parietal bosses; the bridge of the nose is sunken and the cheek bones are high and prominent. There may be a mongoloid slant to the eyes—sometimes with an epicanthal fold. The appearance is referred to as "mongoloid facies." The superior maxilla is enlarged and sometimes results in protrusion of the upper incisors which gives a more "rodent" than "mongoloid" cast to the face. The abdomen is prominent due to splenomegaly and hepatomegaly. Cardiac enlargement is said to begin late in childhood and to slowly increase. According to Smith, *et al.* (5) growth tends to be normal up to about eight or ten years of age after which it is retarded, so that the final stature is short. Development of the secondary sex characteristics is retarded and normal menstruation is rare. Caffey (6) considers Cooley's anemia to be the *best example of skeletal dwarfism and infantilism caused by chronic anemia*.

In thalassemia major hemoglobin F is characteristically present in large amounts. The values usually run between 50 and 90 per cent. The principal hematologic findings are a marked hypochromic microcytic anemia, nucleated red cells, reticulocytosis, leukocytosis, target cells and decreased osmotic fragility of the red cells. Red cell survival is decreased, serum bilirubin is elevated and fecal urobilinogen output is markedly increased. Serum iron is high.

DOUBLE HETEROZYGOSITY

To date at least 22 inherited variants of normal hemoglobin have been detected. Some of these have been found in combination in individuals who are heterozygous for each gene present. Interactions between the gene for thalassemia and a gene for one of the abnormal hemoglobins have been found to occur. Some of these interactions have been described in so few cases that they do not warrant inclusion here. Others, however, show a significant incidence or have a special significance for thalassemia and will be briefly mentioned below.

Thalassemia-Lepore hemoglobin: By means of starch block electrophoresis it is possible to separate Lepore hemoglobin from hemoglobin A. The Lepore hemoglobin migrates between hemoglobin A and hemoglobin A₂ at the same speed as hemoglobin S but it does not cause sickling. Gerald and Diamond (7), in 1958, described a child with thalassemia major whose mother and four of her relatives had the Lepore trait and whose father had thalassemia trait. The blood picture in those with the Lepore trait was like that of thalassemia trait but without elevated A₂ hemoglobin. Hemoglobin A₂ was elevated in the father. Investigation of the mother's family indicated that the Lepore trait was inherited as a single gene effect. On the basis of this study it would seem that the Lepore gene can interact with the classic thalassemia gene to produce a clinical picture like that of thalassemia major. Furthermore, Jonxis (8) has recently reported two cases which appear to represent homozygosity for the Lepore trait. He described two children, clinically and hematologically resembling thalassemia major, whose parents both were heterozygous for the Lepore trait.

Thalassemia-hemoglobin H: Hemoglobin H is an abnormal hemoglobin which on electrophoresis moves more rapidly than normal hemoglobin. H hemoglobin has been observed only in individuals who are also heterozygous for the thalassemia gene. This would suggest that the thalassemia gene activates the expres-

sion of hemoglobin H. The clinical course and severity of this doubly heterozygous state are similar to that of thalassemia minor. Incubation of the red cells with cresyl blue reveals intra-erythrocytic inclusion bodies characteristic of this hemoglobin variant.

Thalassemia-hemoglobin S (microdrepanocytic disease): Double heterozygosity for the genes for thalassemia and hemoglobin S results in a hematologic and clinical syndrome which is designated thalassemia-hemoglobin S disease or sickle cell-thalassemia. This is a clinically important entity which has been found in high incidence in Sicily, Southern Italy and Greece. We have seen a number of such cases in Jamaica, West Indies where Negro-Chinese mixtures are common. Went and Mac Iver (9) have published an excellent report on the thalassemias in the West Indies from the University College Hospital in Kingston. Although thalassemia trait is known to occur in the Negro, most cases of sickle cell-thalassemia reported in this country have been in white patients. In fact, most of the cases previously reported as sickle cell anemia in whites have been found on re-examination to be sickle cell-thalassemias. Several cases, however, have been described in American Negroes (10).

The clinical picture of thalassemia-S disease is subject to considerable variation in different patients and may range from a practically asymptomatic state to one comparable to severe sickle cell anemia or thalassemia major. There may be mild bone and joint pain. Abdominal pain, although severe in some cases is usually not comparable in severity to that which may occur in sickle cell anemia. Hemolytic crises also tend to be milder and less frequent. Splenomegaly and hepatomegaly are fairly constant features. Signs and symptoms due to intravascular sickling may occur but are usually less severe and less frequent than in sickle cell anemia. Splenic infarction as a result of airplane flights (11) and *Salmonella* osteomyelitis (12) have both been reported in this syndrome.

The blood picture is more like that in thalassemia than in sicklemia. There is a hypochromic microcytic anemia, marked decrease of osmotic fragility and many oval and target cells. Sick cells are not usually demonstrable on freshly made blood smears but sickling can be induced *in vitro*. On electrophoresis, hemoglobins S, F and A are characteristically present, although in some cases A may be absent.

Thalassemia-hemoglobin C: Unlike thalassemia-S disease most of the cases of thalassemia-C reported in this country have been in Negroes. It has been found in whites, also, however. The clinical manifestations are usually mild. There is a moderate anemia and mild to severe bone pain. The spleen may or may not be palpable. The blood picture, in addition to showing the characteristics of thalassemia, reveals large numbers of target cells and microspherocytes. There is no sickling. Electrophoresis shows hemoglobins C, A and F. Hemoglobin C usually comprises from 70 to 90 per cent of the total.

Thalassemia-hemoglobin E: This syndrome is common in Southeast Asia. The clinical picture is similar to that of thalassemia major and shows the wide variations in expression we have come to expect from the thalassemia gene. Clinical manifestations are usually manifested during the first year of life. The

blood picture is like that of thalassemia and hemoglobin studies show hemoglobins E and F. Hemoglobin A has been reported to be present also in a few cases.

BONE LESIONS IN THE THALASSEMIAS

The skeletal changes in thalassemia are due, fundamentally, to overactivity and overgrowth of the bone marrow. Erythroid hyperplasia is a response to increased destruction of defective red cells. Marrow hypertrophy widens the medullary cavities and the increased intramedullary pressure results in atrophy of the spongiosa and corticalis (Figs. 1, 2). The shafts of the long and short tubular bones are osteoporotic. Many of the bone trabeculae are destroyed. Others are coarsened. The cortex is thinned (Figs. 3-5). Normal modeling of the bone contour is lost as the hyperplastic marrow flattens or bulges the normally concave surfaces of the shafts. In infants and young children practically all the bones contain red and cellular marrow and the changes resulting from marrow hyperplasia may involve the entire skeleton. They are usually most marked, however, in the short tubular bones of the hands and feet and in the femora (Figs. 6-8). As a rule, *skeletal changes are not very marked during the first year of life* but demonstrable abnormalities in the bone have been observed as early as 4½ months of age. The earliest changes are found in the smaller bones, particularly the metacarpals and metatarsals. *In thalassemia major these changes are generally in excess of those which are usually seen in the other chronic hemolytic anemias such as sickle cell and spherocytic anemia or in the reticuloses.*

In the skull marrow hyperplasia results in widening of the diploic space. The outer table is displaced externally and is often thinned. In some cases it is completely atrophied. Occasionally the diploic trabeculae assume a position perpendicular to the inner table presenting a radial pattern which, when advanced, is referred to as a hair-standing-on-end appearance (Fig. 9). As Caffey (6) has pointed out, there is usually no involvement of the occipital squamosa inferior to the internal occipital protuberance. It appears that the earliest changes in the skull occur most often in the frontal bone (Figs. 10, 11). Skull changes are more common and tend to be more striking in thalassemia major than in the other congenital hemolytic anemias, and, when present, are usually associated in infants and young children with more advanced short tubular bone changes. *The similar skull changes which occur in some cases of iron deficiency anemia are notably unattended by changes in the peripheral skeleton.*

The classic descriptions of the skeletal changes in Cooley's anemia by John Caffey (6, 13) have focused attention on the characteristic changes which may occur in the maxillary, sphenoidal and temporal bones. Overgrowth of marrow in these bones impedes pneumatization of the paranasal sinuses and mastoids and in some cases completely suppresses it. *Inhibition of pneumatization is most evident and most consistent in the maxillary sinuses* and is also frequently noted in the sphenoid sinuses and mastoid air cells. *The ethmoid air cells are not affected* probably because there is little or no marrow activity in the ethmoidal



FIG. 1. Severe thalassemia major. The humerus shows marked erythroblastic swelling of the marrow cavity with loss of the normal contours, thinning of the cortices and osteoporosis. The adjacent ribs are considerably widened.

FIG. 2. Severe thalassemia major. The femur and bones of the foreleg show a generalized osteoporosis. The medullary cavities are widened and the cortices are thinned. The fibula is almost uniform in calibre with rectangular ends.



FIG. 3. Severe thalassemia major. The radius and ulna of a 3 year old child show marrow hypertrophy with loss of the normal contours of the bones. The medullary cavity is widened and the cortices are thinned. There is a mottled osteoporosis. Some of the trabeculae are coarsened, others are atrophied.

FIG. 4. Thalassemia major. The bones regional to the elbow show swelling of the medullary cavities, thinning of the cortices and generalized osteoporosis. At the ends of the bones the trabeculae are coarsened.

bone. Pneumatization of the frontal sinuses shows such wide normal variation that accurate appraisal of the degree of retardation in these sinuses is difficult. Overgrowth of marrow in the upper maxilla may result in swelling of the bone and in older patients may produce serious malocclusion of the jaws. The upper central incisors may be pushed ventrally giving rise to "*rodent facies*" which

Caffey considers to be more diagnostic of Cooley's anemia than the mongoloid facies seen in some of the younger children. Marked swelling of the upper maxilla in some patients may also displace the orbits laterally, increasing the inter-orbital distance and producing ocular hypertelorism. Changes in the paranasal sinuses, mastoids and facial bones are seldom ever seen in sickle cell or spherocytic anemia and although experience with skull changes in iron deficiency anemia is still limited we have not seen them in this condition either. *Retardation of pneumatization of the air cells and swelling of the upper maxilla, when seen, may therefore be considered a paramount point in differential diagnosis with very little risk of error.*

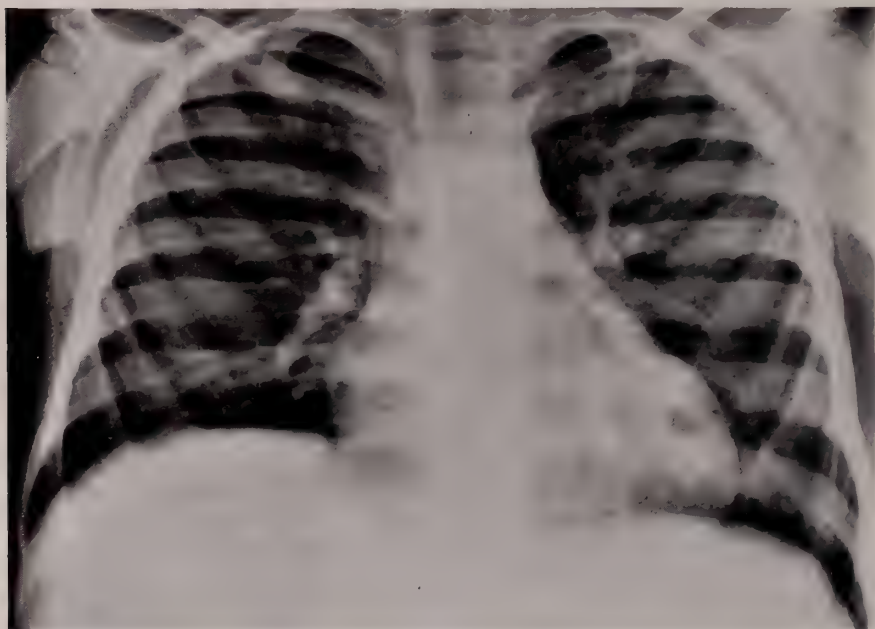


FIG. 5. Ribs in patient with thalassemia major (Cooley's anemia). All of the ribs are widened and osteoporotic and show coarse trabeculation. The cortices are thinned.

Alterations in the spine are limited to reticulation and osteoporosis of the vertebrae. Compression of the vertebrae (cupping) which is so common in sickle cell anemia is seldom seen in thalassemia major.

In patients who survive infancy and early childhood there is a marked regression of the changes in the peripheral skeleton as age advances. With progressing age active marrow recedes from the distal portions of the skeleton towards the trunk and the earlier changes seen in the peripheral bones tend to disappear. In the central segments of the skeleton, however, where red and active marrow persists, the bone changes continue and may, in fact, become more pronounced. *Thus in later childhood and adulthood the skull, spine, and pelvis may show advanced roentgen bone changes while the tubular bones appear normal.* The hands, which are the optimal sites for roentgen diagnosis in

infants and young children, are the least diagnostic parts in older children and young adults. The changing patterns of skeletal involvement with increasing age have been well demonstrated by Caffey (13) in his remarkable longitudinal studies of four patients from early childhood through pubescence into adult life. As age advances retardation of growth and maturation of the skeleton becomes more pronounced.

The bone changes described above may be considered characteristic for



FIG. 6. Hand in severe thalassemia major. The coarse trabeculae in the phalanges and metacarpals form a honeycomb pattern in the swollen bones. The cortices are atrophic. The metacarpals have lost their normal external contours and tend to be rectangular.

severe thalassemia major. But what skeletal alterations might we expect in the other forms of thalassemia and its variants? Reports on the bone changes in thalassemia, including the classic descriptions by John Caffey were made



Fig. 7. Thalassemia major. More moderate changes are noted in the bones of this hand. There is osteoporosis, trabeculation and cortical thinning but the bones have relatively normal external contours.

before the explosive developments in our knowledge of the hemoglobins and their genetics had become fully appreciated and utilized. Hence it was not possible to correlate the roentgen bone changes with the heterozygosity or homozygosity of the syndromes described or with the composition of their hemoglobins. The recent literature on the syndromes produced by the newly discovered

FIG. 8. Thalassemia major. The femur shows swelling at its distal end with cortical atrophy and some coarsening of the trabeculae.



hemoglobinopathies is exciting but significant descriptions of the bones of these patients are usually lacking. In those rare reports where some small comment is made regarding the roentgen skeletal findings, the bones have been described in the most general terms, usually merely as showing some osteoporosis.

It is apparent, however, that thalassemias other than severe thalassemia

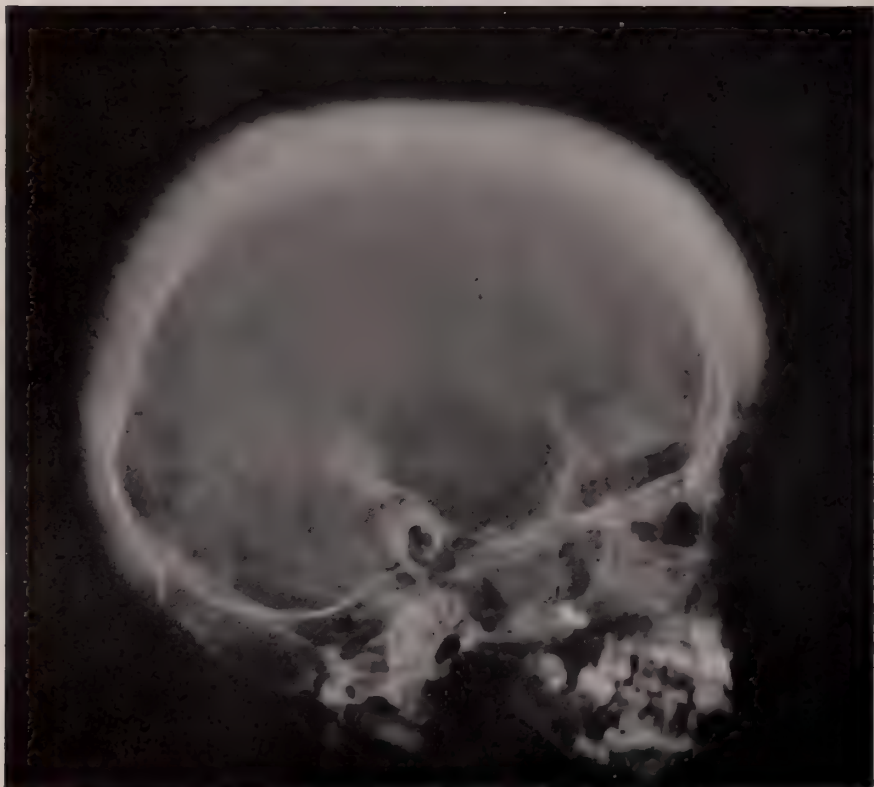


FIG. 9. Classical hair-standing-on-end appearance of the skull in the homozygous state of thalassemia. The diploic space is considerably widened in the frontal, parietal and occipital bones. There is a conspicuous absence of such changes, however, in the occipital squamosa inferior to the internal occipital protuberance. The outer table of the skull is atrophied and the diploic trabeculae assume a position perpendicular to the inner table. There is a granular osteoporosis of all of the bones. The maxillary sinuses are not pneumatized due to swelling of the bone. The ethmoid cells show aeration. Lack of pneumatization of the maxillary sinuses should differentiate this condition from the other hemolytic anemias.

major can produce significant alterations in bone structure. No roentgen skeletal changes have been described in thalassemia minima or trait but in Rietti-Greppi-Micheli disease, which is a heterozygous form of thalassemia with moderate anemia and sometimes with mild and intermittent jaundice, marked osteoporosis without gross anatomic distortion has been described (3). Bone changes would be expected also in some of the "intermediate" forms of thalassemia since these represent heterozygous thalassemia of greater severity than Rietti-Greppi-Micheli disease, a moderate type of thalassemia major or double

heterozygosity for thalassemia and an abnormal hemoglobin. Wintrobe (12) has described a case of thalassemia minor in an eighteen year old boy in whom there was osteoporosis and thinning of the cortices of the long bones. Caffey (13) has described changes in an exceedingly mild case of thalassemia. His patient led an essentially normal life until her second pregnancy at the age of 25 when a severe anemia developed requiring blood transfusions. She had been observed and studied intermittently since the age of 8 because hemolytic anemia had been detected in her brother. Follow-up roentgen studies between the ages of 8 and 25 showed no roentgen abnormalities of the distal portions of her

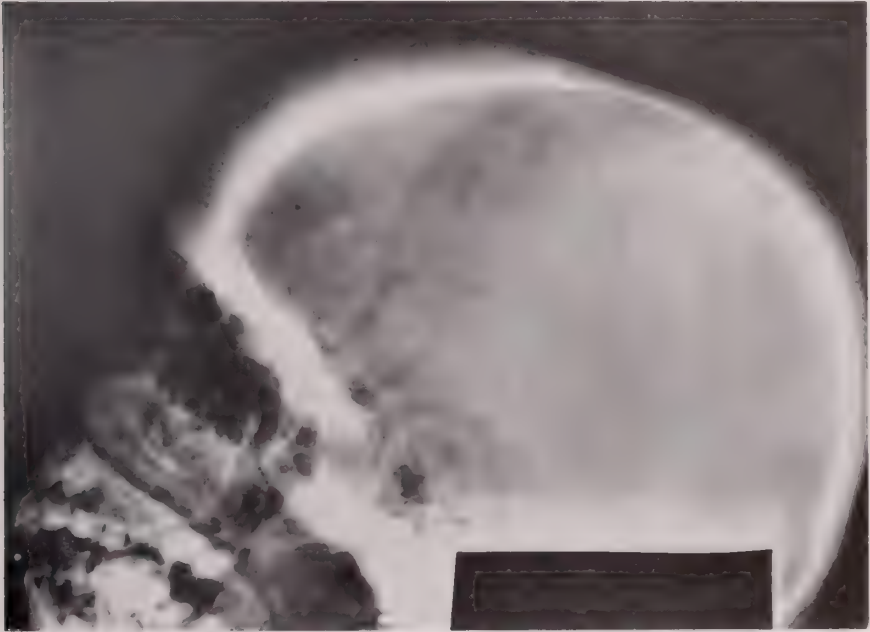


FIG. 10. Skull in thalassemia major. The diploic widening is most marked in the frontal bone. The bones show a granular osteoporosis and pneumatization of the maxillary sinuses is retarded. The ethmoid cells are well aerated. The upper maxilla is swollen.

skeleton but changes in the skull and spine became more conspicuous as age increased. This was certainly a very mild thalassemia and the patient may have been heterozygous, a double heterozygote or an unusually mild homozygote. In spite of the paucity of published data on bone changes in other than the severe type of thalassemia major *radiographically demonstrable bone abnormalities occur in some of the milder forms of the condition including thalassemia minor.*

Thalassemia-Lepore hemoglobin: Descriptions of this syndrome are as yet scarce but it appears that interaction between the Lepore trait and thalassemia trait produces a syndrome similar to that of thalassemia major although perhaps less severe. A moderately severe hemolytic anemia, moderate splenomegaly and bone changes resembling those of thalassemia major have been reported (7).

Thalassemia-hemoglobin H: The clinical course and severity of this syndrome is like that of thalassemia minor and although there have been no reported studies of the bones it seems likely that in the more severe cases bone changes would be similar to those which may be seen in the more severe grades of thalassemia minor.

Thalassemia-sickle cell disease (microdrepanocytic anemia): When bone al-

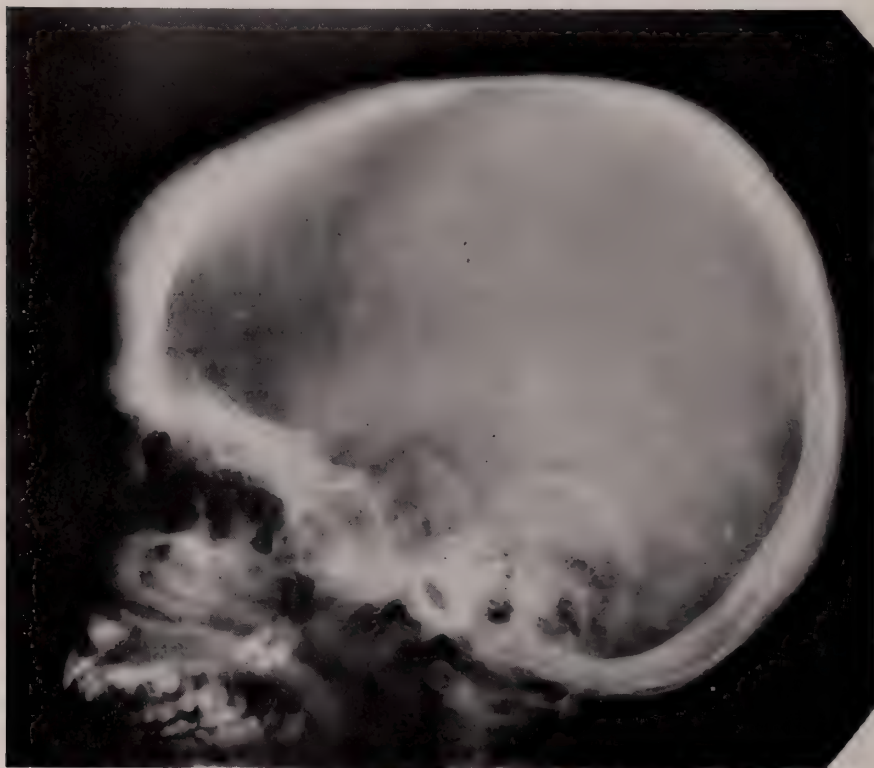


FIG. 11. Skull in thalassemia major. Widening of the diploic space is most marked in the frontal bone and absent inferior to the region of the internal occipital protuberance. Pneumatization of the maxillary sinuses is almost completely suppressed. The upper maxilla is swollen but significant ventral displacement of the central incisors has not yet occurred.

teration occurs in this syndrome it may simulate in every respect the patterns of bone change seen in sickle cell anemia and sickle cell-hemoglobin C disease. Most cases have shown either no change or varying degrees of osteoporosis without gross distortion of the osseous contours or trabecular markings. On occasion, however, there may be aseptic necrosis of the proximal end of the femur or humerus and in older patients spongiosal sclerosis and thickening of the inner aspects of the cortices of the long bones may be seen. We have seen this in a few unreported cases and reports of such changes have been made by Reich and Rosenberg (14) and by Powell, *et al.* (15). In addition, *Salmonella* osteomyelitis has been reported in this thalassemia variant (12). This compli-

cation occurs with surprising frequency in sickle cell anemia and has been reported in hemoglobin C-D disease in which there is no sickling (12). The cause of an unusual incidence of *Salmonella* osteomyelitis in patients with abnormal hemoglobin disease is still a matter for speculation but it would seem likely that it is related to a deficit in the blood supply to the affected bones.

Thalassemia-hemoglobin C: Reports of this condition have been few. The clinical manifestations are apparently mild and no significant bone changes have been described to date.

Thalassemia-hemoglobin E: The clinical manifestations of this syndrome may be moderate or severe and in many instances are indistinguishable from those of thalassemia major. Chernoff, *et al.* (16) have described the clinical and hematological findings in 32 patients with this double heterozygous state seen in Bangkok, Thailand, but have made no comment on the skeletal changes. Since the condition is often severe with marked clinical resemblance to thalassemia major it is to be expected that bone changes similar to those seen in Cooley's anemia would occur in varying degrees of severity and extent. This has been demonstrated in two recent reports. Van Dijk (17) has reported two Indonesian children with thalassemia-hemoglobin E disease in whom the clinical symptoms were similar to those of thalassemia major. Both children showed bone changes indistinguishable from those of Cooley's anemia. In one, the widening of the diploic space in the skull was accompanied by vertical striation of the trabeculae. Klefstad-Sillonville *et al.* (18) have described six Cambodian children with this double heterozygous condition, all of whom also showed skeletal changes similar to those of thalassemia major.

Routine roentgen skeletal surveys on all patients with abnormal hemoglobin syndromes is much to be desired. It is likely that the paucity of information on bone changes in these syndromes is due to the fact that some of them have been found in areas where radiographic facilities are limited or conditions are not conducive to large scale x-ray studies. In addition, the sudden impact of the exciting developments in our knowledge of the hemoglobinopathies has served to focus attention on the molecular structure and genetic background of the abnormal hemoglobins. It is expected that in time radiographic studies of sizable groups of patients will be reported and classifications of syndromes will be refined so that our knowledge of the associated bone changes will be placed on a more substantial basis.

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THE RATIONALE OF DRUG SELECTION IN TUBERCULOSIS THERAPY*

CARL MUSCHENHEIM, M.D.

New York

The specific drug therapy of tuberculosis is now in its sixteenth year of general clinical experience. A vast literature has accumulated in the decade and a half since the introduction of streptomycin and in the decade since the introduction of isoniazid. These two antimicrobial agents still stand as the principal elements in the armamentarium which has so effectively revolutionized the therapeutic management of the disease. This simple fact is hardly one to be brought to the attention of a group such as this, which includes so many of the pioneers and outstanding experts in the field. Nevertheless, we can perhaps all benefit by taking stock of the present situation and reflect on where we stand, and in what direction we may be going. I hope that you will bear with me, therefore, if I begin by reviewing some basic considerations and then proceed to outline the schema which appeals to me personally in the therapeutic approach to this disease.

BASIC CONSIDERATIONS

It is fundamental that in the treatment of tuberculosis, as in that of any other disease, we must constantly weigh the benefits of therapeutic efforts against the possibilities of harm which these may do. Everyone, I am sure, agrees with this, yet the literature abounds with recommendations based on statistical analyses of various criteria of therapeutic success, with little attention to the balancing factors of harmful side effects. An example of this is a recent report from Birmingham, England, entitled "100% Sputum-Conversion in Newly Diagnosed Pulmonary Tuberculosis" (1). Apparently inspired by the work of Professor Crofton of Edinburgh, these workers selected from a larger number of patients admitted to three chest hospitals those who had bacterial resistance tests made on admission. The study group numbered 530 patients whose primary cultures were susceptible to at least two of the three standard drugs (*i.e.*, isoniazid, streptomycin and PAS). The 100 per cent conversion claim is made for those who were treated according to Crofton's plan of giving initially all three drugs until the results of susceptibility tests are known. Five patients who died of tuberculosis were excluded, with the justification that they died within a month. The conversion rate was therefore not in actuality quite the 100 per cent claimed in the title. Furthermore there is lacking any mention whatever of toxic reactions. Similarly in Crofton's own report, published a year earlier, of 240 patients treated in the same way and all attaining sputum conversion, there is no record of the toxic manifestations (2). His exclusion of three patients

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is justified on the basis that they died of other diseases. In one instance the other disease was agranulocytosis, but the possibility that this might have been the result of drug-toxicity appears not to have been entertained. Can we conclude from these two reports that the only untoward reactions among nearly 800 patients receiving all three drugs for at least several months was a single possible case of agranulocytosis? Or is it more reasonable to assume that other toxic manifestations occurred, some possibly serious. In this connection the Birmingham group excluded in addition to the five early deaths from tuberculosis, another seven patients who died of diseases other than tuberculosis, but they did not state what the diseases were. Regardless of whether any of these might have been iatrogenic, we all know that even when not fatal drug reactions may often be very serious; more serious by far than failing to achieve sputum-conversion within a year. I do not wish to dissect these reports in an unfriendly manner, but there are three important points to be made. First, it seems probable that among 800 patients there was in fact a significant incidence of important toxic reactions, but that these were not regarded as particularly important in contrast to the real or supposed hazards of failure to achieve prompt conversion and possible emergence of drug resistance. Second, in the Birmingham study 36 patients had resectional surgery despite the conversion. The point which was emphasized, that conversion occurred *prior* to surgery, is not necessarily a consideration of overwhelming importance. Third, in the Birmingham study the incidence of infection primarily resistant to isoniazid was only 0.5 per cent, and primary resistance to the other major drug, namely streptomycin, at 1.5 per cent was not much higher. Furthermore, the figures the world over, with the exception of some doubtful reports, indicate that primary drug resistance remains at a relatively low figure. For instance, the overall incidence reported by Fox *et al.* in 1957 of 5 per cent primary resistance to at least one of the three standard drugs, is by no means an alarming figure (3). A recent report by Chaves and his associates shows some increment in the past five years in primary drug resistant infection in New York City, but not enough to make this as yet a very important consideration in the selection of an initial drug regimen (4).

The two reports on "triple" drug therapy which I have just cited from the literature are perhaps extreme examples of focusing on criteria of therapeutic success, indeed, in these instances, on but a single criterion, and disregarding other factors which should be considered. We have, however, many other examples of dwelling on a few percentage points of difference in conversion-rates and neglecting the incidence of toxic reactions, even when these are recorded. If one considers *allergic* reactions alone, Kalinowski and his co-workers found among more than 3,000 patients analyzed for drug toxicity an incidence of 7.2 per cent reactions to PAS, 5.8 per cent to streptomycin and only 0.1 per cent to isoniazid (5). In our own experience also, allergic reactions to isoniazid alone are extremely rare, but a double allergy to both PAS and isoniazid, when these are administered concurrently is, I believe, higher than the 0.1 per cent figure just quoted. Indeed, when allergy develops on an isoniazid-PAS regimen it is, in

my own experience, more common to both drugs than to PAS alone. These double allergies are often extremely serious, not infrequently progressing to severe hepatitis and toxic encephalopathy. The evidence suggests that such hypersensitivity reactions are most often primarily due to PAS. Isoniazid and probably also streptomycin evoke the reactions rarely unless they are initially triggered by concurrently administered PAS. The incidence, I am quite sure, is higher than reported because frequently the onset is insidious and the entire illness, even to a fatal termination, may be misdiagnosed. Isoniazid with PAS is, as I think will be accepted by everyone, a regimen of significantly higher risk than isoniazid alone. Streptomycin in any combination is potentially damaging, especially to patients in the older age group, and if administered daily. Unless administered daily, as Crofton has emphasized, and quite rightly, it is not used to its best therapeutic effect.

All the evidence indicates that there is a significantly greater toxicity problem whenever multiple-drug regimens are employed in place of isoniazid by itself. Despite this there has been for years an insistence that in tuberculosis therapy at least two drugs should *always* be used; more particularly that in initial regimens there should be administered isoniazid plus either PAS or streptomycin, if not both. One may agree that *when* two drugs are required in an initial regimen it should be isoniazid plus one of these other two. Certainly none of the several other agents, usually classed as secondary drugs, has yet proved as advantageous as a companion to isoniazid. But let us examine a little further the rationale for two-drug regimens.

It has been stated, and the belief is held firmly by many, that the superiority of a multiple-drug regimen is based on the delay which is observed in the emergence of bacterial drug-resistance. This belief has been dramatized in the words of Crofton that "the greatest disaster that can happen to a patient with tuberculosis is that his organisms become resistant to two or more of the standard drugs" (2). The corollary to this thesis is that testing for bacterial drug resistance is an essential guide to therapy, and that the drug or drugs should be changed when an appreciable shift occurs toward a higher proportion of drug-resistant bacterial cells.

A clinical correlation between the emergence to predominance of bacterial drug resistance and therapeutic failure was, in fact, very clearly demonstrated in the early days of streptomycin therapy. So also was a correlation between prolongation of the therapeutic efficacy of streptomycin by the addition of PAS. On the basis of clinical observations, as opposed to animal experiments, this is where the matter still rests. The complexities of isoniazid-resistance and of testing for isoniazid-resistance are so much greater that similarly clear correlations have never been convincingly shown. This is not to say that isoniazid-resistance may not be a limiting factor in therapy, nor that isoniazid combined with another drug may not be therapeutically more effective than when it is administered independently. There is evidence, however, that: 1) it is more importantly because of other mechanisms of re-inforcement than by delay of resistance, that the two-drug regimens are in certain circumstances superior

in clinical results, and 2) we do not with the routine methods of *in vitro* testing usually know where we stand as regards isoniazid resistance. Taking the second point up for discussion first, there is absolutely no agreement with regard to the level of *in vitro* resistance which is clinically significant in terms of impairment or loss of antimicrobial efficacy. Canetti has prepared an interesting table of the frequency with which over one hundred strains of tubercle bacilli he tested would be classified as resistant or susceptible depending on eight different criteria used in various laboratories (6). The frequency ranged from 99 per cent of strains characterized as resistant down to only 25 per cent. The differences in criteria related not only to the definition of the critical concentration of isoniazid (which ranged from 0.1 mc/ml to 5.0 mc/ml), but also to the abundance of the required culture on the critical concentration compared to that on the control tubes. Even these eight different criteria of Canetti do not represent *all* the variations in routine susceptibility testing, nor do any of the methods used routinely define the actual proportion of resistant cells in the primary isolate. With respect to isoniazid, therefore, the clinician obtains information of rather limited significance from the reports he receives of susceptibility tests. He learns only what he already knows, that failure of conversion is associated in time with the appearance of more resistant cells in the subsequent cultures than were present in the initial cultures. From clinical observations he knows also that such shifts in the bacterial population do not necessarily preclude later conversion without change in therapy, and that the tempo of progression of the disease usually continues to be restrained by isoniazid even when high degrees of resistance are demonstrated *in vitro*. The emergence to predominance of resistance to isoniazid may be regarded more as a consequence of therapeutic failure than actually its cause. Lest this be considered a mere quibble, let me add that the point is not that failure of conversion is unimportant but that it is not necessarily the unmitigated disaster it is often alleged to be. We cannot say that the state of "open negativity" (which is attainable more often with a regimen of isoniazid and daily streptomycin, for instance, than with isoniazid and PAS); we cannot say that this state of "open negativity" is a prime objective of initial therapy until we know a great deal more about the after-history of open negativity than we do at present. If the need for surgery is actually eliminated by attainment of the open-negative state, then the approach to a 100 per cent conversion-rate will be more important than if we find in longer follow-up observations that late relapse is significantly common, or that persistent open cavities are significantly liable to nontuberculous complicating infections. There are indications already that both these difficulties may be expected. Conceivably one could do better with a slightly lower conversion-rate than is attainable by isoniazid-streptomycin, or the triple therapy recommended by the British groups, if streptomycin is withheld in the initial regimen and reserved for the time of surgery. In this connection the cavity closure-rate with any of the known regimens is nowhere near the 90 to 100 per cent sputum conversion-rate attainable by either of the two-drug regimens, and by isoniazid alone in properly selected cases.

Returning now to a consideration of the superiority of two-drug regimens containing isoniazid over isoniazid alone, this superiority is documented principally with regard to conversion rates in "open" forms of tuberculosis, such as cavitary pulmonary tuberculosis and renal tuberculosis. From experimental work it is known that there is actually mutual enhancement of antimicrobial activity by isoniazid and streptomycin *in vivo*. This has been shown in the experiments of McCune and Tompsett, by the use of bacterial enumeration techniques in mice (7). A lesser enhancement of isoniazid by PAS has also been shown in the same experimental model. Evidence has been advanced, particularly by the groups working in Denver, that PAS is effective in blocking the partial inactivation of isoniazid by acetylation. This effect, however, has not been confirmed in the chemical assays of Peters, which undoubtedly are more precise than the bio-assay methods on which the original conclusions were based (8). The matter is, therefore, in doubt, but this is another possible mechanism by which PAS may reinforce the therapeutic efficacy of isoniazid. McDermott has advanced the thesis that it is more importantly the enhancement of antimicrobial action against microbial cells susceptible to both drugs, which is responsible for superiority of certain drug pairings (including those presently under discussion), than action of the second drug against cells resistant to the other (9). The result may be the same, as regards a reduction in the eventual incidence of predominantly drug-resistant cells in the infection, but the point is that no combination of drugs actually eliminates all drug-resistant cells. Neither does it eliminate all drug-susceptible cells. This has been shown experimentally, by McDermott and McCune, as the phenomenon of *persistence* of drug-susceptible cells even after treatment with the most potent combination of drugs, namely isoniazid-pyrazinamide (10). A significant clinical observation, which relates to the problem of isoniazid-resistance as a limiting factor in isoniazid therapy, is one which was made at the very start of the clinical investigation of isoniazid (11). This is that in the isoniazid therapy of miliary tuberculosis the neutralization of drug-effectiveness due to drug resistance does not occur, in contradistinction to what was observed frequently with streptomycin. The only isoniazid-treated patients who received a second drug in these early trials were several with hyperactive infections whose early response was doubtful and streptomycin was added after a week or two; or those who already had a complicating meningitis. No isoniazid-treated miliary tuberculosis patients, among those treated with isoniazid alone, relapsed under treatment. Nor did meningitis develop in any.

Thus, on both experimental and clinical grounds, it may be said with considerable assurance that in the selection of a program of initial drug therapy it is not primarily the problem of drug-resistance with which one is concerned. Rather, the primary concern is the attainment of optimal therapeutic benefit for the *particular clinical form* of tuberculous infection, with a minimum risk for the *particular individual* who is to receive the drug or combination of drugs. For most cavitary pulmonary tuberculosis it has been abundantly shown that multiple-drug regimens are superior to single-drug therapy with isoniazid; in terms

particularly of sputum conversion, but also to some extent in terms of extent of resolution of reversible components, closure of cavities and appearance of new foci of disease. These superiorities are statistically significant but actually are not extremely large. Against them should be balanced not only the increased risk of toxicity, but even the risk of multiple drug-resistance in the event of failure as opposed to the risk of drug-resistance only to isoniazid. I know of no evidence that triple-drug therapy in pulmonary tuberculosis is superior by any criteria to isoniazid-streptomycin (if streptomycin is administered daily). Yet there are seen occasional failures on this regimen, despite initial bacterial susceptibility to both drugs.

SCHEMA OF INITIAL THERAPY

I first presented a schema of treatment in tuberculosis in 1955 (12). In some respects this was regarded at the time as an heretical, if not a downright reckless disregard of established principles. However, there has been little that has transpired in the interval that leads me to change the main features of the program, nor to alter importantly any of the details. On the contrary, some of what appeared unacceptable to many six years ago has come to receive at least limited approval.

In brief summary, the selection of regimens is as follows:

A) *Isoniazid alone*—for minimal pulmonary tuberculosis and for certain "closed" forms of tuberculosis such as pleurisy with effusion, tuberculosis of lymph nodes, tuberculous peritonitis of the acute serofibrinous type, tuberculous salpingitis uncomplicated by chronic pelvic peritonitis, lupus vulgaris, and some other forms which experience shows respond readily and quite regularly to therapy of submaximal potency.

B) *Isoniazid-PAS* for most patients in the older age group with cavitary pulmonary tuberculosis or in other forms for which in younger patients one would administer isoniazid-streptomycin. Meningitis is probably not adequately treated with isoniazid-PAS, so that an exception might be made of this as regards treatment at any age.

C) *Isoniazid-Streptomycin (daily)*—for cavitary pulmonary tuberculosis in younger patients and, in these, for such severe or potentially damaging forms as meningitis, pericarditis, bone and joint tuberculosis and genito-urinary tuberculosis. Miliary tuberculosis also should be treated with this regimen, mainly because of the chance, however small, of primary resistance to isoniazid.

D) *Isoniazid-Streptomycin-PAS*. This "triple" regimen has in my opinion very little usefulness. If streptomycin is given daily it is doubtful that even in renal tuberculosis, in which the triple regimen has become more or less standard, the addition of PAS is important. I think, however, that renal tuberculosis is the one situation in which a triple regimen (with streptomycin given less frequently than every day) may have merit. The likelihood of renal functional impairment, as the result either of extent of involvement or of hydronephrosis from complicating ureteral strictures, may make full dosage of streptomycin somewhat more hazardous than usual. Perhaps this regimen also has a place for

older people with severe infections for whom one might desire something more than isoniazid-PAS but does not wish to run the risks of intensive streptomycin therapy. It must be appreciated, nevertheless, that committing streptomycin in submaximal dosage involves the most definite risk known of loss of drug-effectiveness as the result of bacterial resistance. A high degree of demonstrable streptomycin resistance, by the usual clinical laboratory tests, may certainly be taken as evidence that the drug will be no longer effective; particularly if this is found in cultures from more than a single specimen.

With these possible exceptions, then, I find no indication for triple-drug therapy as an initial regimen. I am not convinced that 100 per cent sputum conversion is actually to be expected from it with great consistency, nor from any combination of drugs. Moreover, 100 per cent conversion rates are approachable with other regimens designed on a more selective basis.

CONTINUATION THERAPY

There have been no studies designed specifically to determine for how long the companion drug to isoniazid should be continued once the therapeutic objectives have been attained. It seems probable that methodical investigation would show that the companion drug could be safely discontinued soon after the so-called "target point" of cavity closure and sputum conversion. The matter is perhaps of relatively small importance, since the more serious toxic manifestations usually occur early. However, simplification of therapy is always desirable and this question should be answered.

The addition of streptomycin to an initial isoniazid-PAS regimen is a consideration, more often than the addition of PAS to an initial isoniazid-streptomycin regimen. In either case there is little reason to stop the isoniazid. Most clinicians, in this country at least, agree that isoniazid once begun had best be continued as long as the disease is active, and for one or two years afterward, unless it must be stopped for reasons of toxicity.

RETREATMENT PROBLEMS AND SECONDARY DRUGS

There is little to be gained in a discussion such as this from reviewing the secondary drugs, or the particular indications for one or the other in retreatment problems. The only point which I should like to emphasize in this connection is that I am sure one is on firmer ground if one is guided by clinical observation than if one looks mainly to the laboratory reports of susceptibility tests. Even in retreatment, isoniazid is probably the most useful drug of any, regardless of how it may have been used before. The program is, therefore, best built on this as the keystone. A further, and final, observation, and one with which I fear many may disagree, is the following: the best solution of retreatment problems is, of course, their prevention by a well-designed and conducted initial treatment program, but it is more often discontinuity of treatment than it is the particular regimen selected initially that is responsible for failures and subsequent problems of retreatment and drug resistance. One may, for instance, treat cavitory tuberculosis initially with isoniazid alone. By the addition of

streptomycin and PAS later, only if and when needed, and by the performance of surgery soon thereafter, if this also is needed, one will come out at the end of a year about as well as with any other program. Our group treated a series of moderately and far-advanced cases in just this way a few years ago (13). Two-thirds of them never needed anything more than isoniazid. Complete therapeutic success was attained by the end of a year in 90 per cent, not just sputum conversion but also closure of cavities or their elimination by surgery. I think that one can do better than this in cavitory tuberculosis by starting with a two-drug regimen; but not a great deal better, and certainly there were no disasters even though there was some *in vitro* evidence of isoniazid-resistance. This is not now, and never has been, recommended by us as the preferred treatment for cavitory pulmonary tuberculosis. Nevertheless, the study demonstrated the great effectiveness and reliability of isoniazid in prolonged initial treatment, even when administered without a companion drug.

In conclusion, the accumulated evidence indicates that in the treatment of tuberculosis individualization is of the greatest importance. Despite many gaps in our knowledge there is a large quantity of information which permits the formulation of a sound rationale for the selection of an optimal drug regimen for each particular circumstance of tuberculosis therapy.

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THE PREPARATION OF SUBCUTANEOUS GASTRIC POUCHES OF THE HEIDENHAIN AND BICKEL TYPES*

FRANKLIN HOLLANDER, Ph.D., VERNON A. WEINSTEIN, M.D., AND
JAMES F. CEREGHINI, B.S.

According to the classical procedures for preparing vagotomized (Heidenhain) and completely neurectomized (Bickel) stomach pouches in dogs, the auxiliary stomach is left in the peritoneal cavity and its open end is delivered through a lateral incision in the abdominal wall. In the case of the former, the vagotomy is effected by transection of the entire wall of the stomach, thus retaining the entire sympathetic supply to the pouch. As originally described by Bickel and Katsch, their pouch was prepared by sympathectomizing a Heidenhain pouch; the blood vessels to this viscus were carefully isolated, and the fine nerves running along their surfaces were torn across with a fine blunt instrument (1). The authors commented that this is a delicate procedure which requires special skill in order not to damage the vessels, and not to prolong the operation unduly. For this reason, and also because of the possibility of missing some of the nerve fibers and thus failing to effect a complete sympathectomy, we became interested in the possibility of utilizing a simpler technique for the preparation of a completely neurectomized pouch of the corpus of the stomach.

In 1925, Ivy and Farrell reported briefly on a two-stage method for the subcutaneous transplantation of gastric pouches in dogs, a procedure which resulted in sympathectomy as well as vagotomy of the auxiliary stomach (2). During the first stage, a single epiploic artery and vein were left in communication with the pouch, and these were transected between ligatures and peritonealized in the second stage of the operation. Only bitches which had recently whelped were used, and the subcutaneous transplant was set in a cavity in or adjacent to a mammary gland. Following this second operation, sloughing occurred in two of five animals so prepared. The technique employed by Gregory and Ivy in 1941 was essentially the same, except for certain details designed to prevent such sloughing (3). These included removal of fat and omental coverings of the pedicle, in the first stage of the procedure, without injuring the blood vessels, and gentle rubbing of their exposed coats with gauze moistened with alcohol. According to the investigators, "the subsequent fibrosis leads to a gradual diminution in blood supply from this source, causing the transplant to rely to an increasing extent on the new vessels growing in from the surrounding tissues." Transection of the pedicle was performed ten or more weeks after the first stage, and then only if clamping the pedicle with the fingers failed to cause blanching of the mucosa of the pouch mouth. Otherwise, the pedicle was stripped as before and inspected again about a month later. Usually, though not in-

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From the Gastrointestinal Physiology Research Laboratory, and the Department of Surgery, The Mount Sinai Hospital, New York, N. Y.

variably, ten weeks was a sufficient lapse before division of the pedicle to effect sympathectomy. However, mention was made of two animals in which the transplant became gangrenous and sloughed a few days after the first stage of the operation. Recently, Schofield reported his use of the technique of Ivy and Farrell, for preparation of transplanted Heidenhain pouches, with two minor modifications: a) the pouch was inserted in a space between the rectus muscle, medially, and the external and internal oblique muscles, dorsally and ventrally; and b) the pouch surface was rubbed with gauze before its insertion (4).

It is interesting, and probably significant of the success of Gregory's procedure, that in his subsequent work he adopted a wholly different technique for sympathectomizing the nonvagal pouch (5). The spleen was resected by ligation of its blood vessels close to the hilum, so that vascular communication between the splenic blood vessels and the pouch was not interrupted. These vessels were then traced towards their origins, where they were cleaned of connective tissue and nerves for a distance of about two cm. Denervation in this way, in contradistinction to that employed by Bickel originally, is easy because of the large size of the blood vessels and because the nerves are here collected into a few large bundles and so easily removed.

Our own technique for preparation of such subcutaneous* Bickel-type pouches is simpler than that previously described and, in our experience with nine dogs, it has been entirely successful in eight. One of the nine, the only one to be converted in less than six months, had a penetrating ulcer one inch in diameter on the posterior wall of the pouch. This ulcer was somewhat irregular in outline but the mucosa at the edges was pink and healthy, as was the remainder of the pouch mucosa. In this instance the pouch had been a subcutaneous Heidenhain pouch for 4½ months prior to its conversion to a Bickel pouch. Within a few days after conversion, bloody, highly acid drainage appeared from the pouch stoma, indicating the onset of ulceration. Whether the ulcer resulted from localized ischemia following the division of the vascular pedicle, or from trauma to the pouch at or subsequent to the time of conversion, cannot be stated with certainty. However, the latter cause is highly probable, because several of our subcutaneous Heidenhain pouches have also developed such ulceration, with penetration into the subcutaneous sac. These lesions occurred at considerable time intervals following the operation, and we have always ascribed them to trauma by a catheter while in use.

Regarding the subcutaneous Heidenhain pouches, our experience has been very large, and equally satisfactory. Because the successful preparation of both varieties of auxiliary stomach involves certain technical problems, as evidenced by the many inquiries which we have received concerning the details of our surgical procedures, we are describing these in the present report.

PREPARATION OF A SUBCUTANEOUS HEIDENHAIN POUCH

The abdomen is opened through a midline incision from the xiphoid to about one inch below the umbilicus, entering the peritoneal cavity to the left of the

* We prefer to characterize these pouches as "subcutaneous" rather than "transplanted" because the former designation indicates in some measure the site of transplantation.

falciform ligament in order to avoid the fat pad enclosed within this peritoneal fold. The stomach and spleen are brought to the skin surface. A portion of the greater curvature, approximately 4 inches in length and 1.5 to 2 inches in width, is selected for the auxiliary stomach. Caution must be taken in planning the limits of the pouch lest an area of constriction be produced in the remaining antrum, between the line of closure and the lesser curvature at the re-entrant angle.* The uppermost margin of the pouch must be above the *vasa brevia*. At the extremes of the contemplated pouch, the omentum is divided and the lesser peritoneal sac is entered with two rubber-covered clamps, so placed as to control bleeding from the gastric wall and spill from the gastric lumen. The stomach is divided between these clamps, thus completely separating the walls of the pouch from those of the residual stomach. We now make this incision along a curved line, concave to the greater curvature, as we found that when a straight line was used, the resulting pouch tends to become J-shaped, and does not drain completely during subsequent experiments. The pouch derives its blood supply solely from the short gastric and left gastroepiploic branches of the splenic artery, and therefore these must be carefully preserved. The stomach and pouch are then closed in two layers, using continuous sutures of chromic catgut for the mucosal surface and silk for the seromuscular layer.

The skin of the left side of the abdomen is now mobilized to create a space between subcutaneous fat and deep fascia. For this purpose, a point on the left flank, most convenient for future collection from the pouch, is selected as the site of its stoma. This point must be far enough posterior to avoid the rib cage, but not so far as to exceed the extensibility of the vascular pedicle. Using the main wound as a starting point, the skin and subcutaneous fat are elevated from the deep fascia laterally. This subcutaneous space may be unroofed by incising the skin at right angles to the main wound and reflecting it as a triangular flap (Fig. A). This maneuver facilitates subsequent placing and fixation of the pouch. Excision of one of the nipples is sometimes necessary, in order not to interfere with future collection of secretion. A stab wound is then made through the fascia, muscle, and peritoneum at a point so chosen that the vascular pedicle of the pouch, passing through this opening, will reach the subcutaneous space without tension. This stab wound is made sufficiently large so that the pouch can be drawn through without traumatizing it or its vascular pedicle. Once this has been accomplished, the stab wound is closed sufficiently to prevent herniation of intraperitoneal content and still not constrict the pedicle. The pouch is positioned (Fig. B) so that the wide end is lateral and the narrow end medial, and it is then anchored in place with about four interrupted chromic sutures on each side, taken between the seromuscular coat and the fascia of the abdominal wall. Again, care must be taken during this step to avoid injury to the vascular pedicle.

A stoma is now established on the ventral surface of the pouch, close to its medial (narrow) end (P in Fig. B). This will be the most dependent point of the auxiliary stomach when the animal is standing upright. A small incision is

* Dr. Allan Kark of this Hospital avoids the possibility of such constriction in the main stomach by closing the defect in the transverse direction.

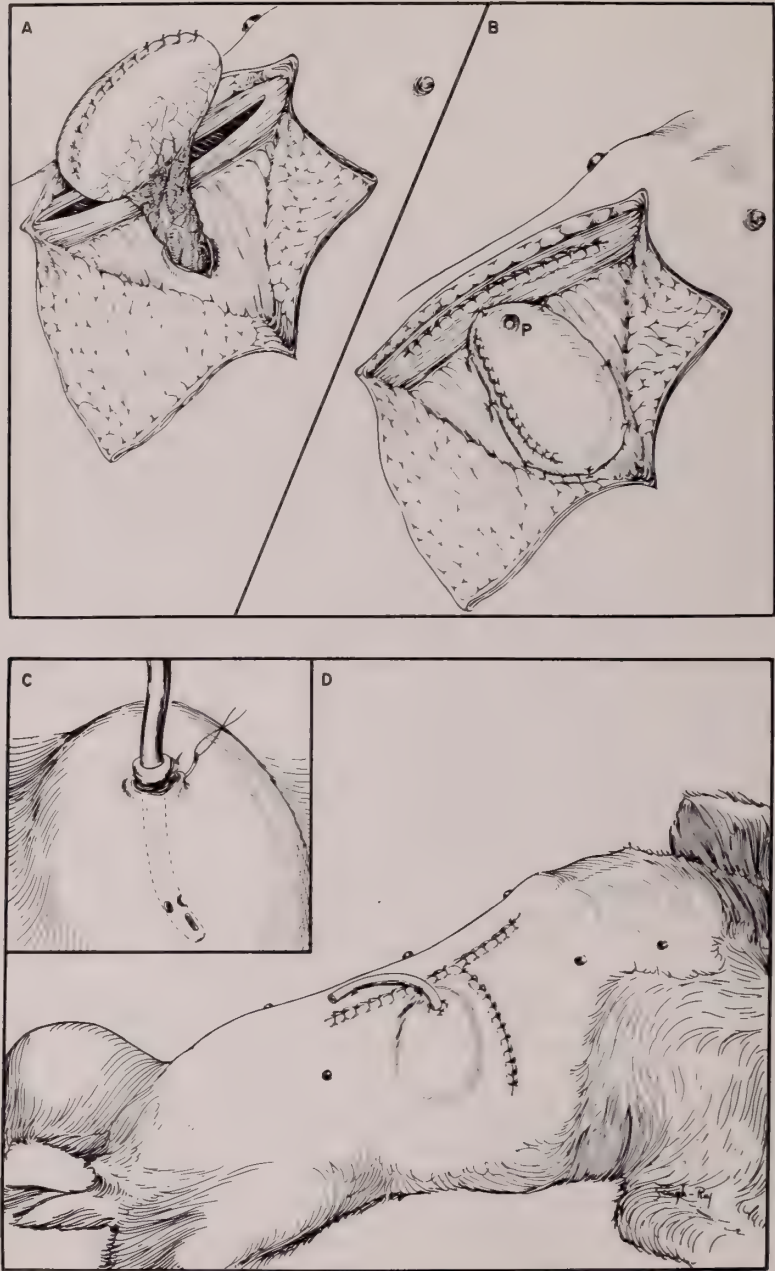


FIG. 1 (A-D). Steps in the preparation of subcutaneous pouches of the Heidenhain and Bickel types.

made into the pouch through its seromuscular coat, at a position free of obvious blood vessels. The stoma mucosa is freed by carefully teasing it away from the muscle, and additional mucosa may be teased out as well, the whole being opened to form a rosette (Fig. C). The size of this opening is such that a #18 French catheter fits snugly. The skin is then closed over the pouch (Fig. D) and the stoma brought to the surface through a separate small incision placed immediately over the mucosal rosette. The stoma is sutured to this skin opening with interrupted fine chromic sutures taken between serosa and skin, the mucosal lip being allowed to protrude above the skin surface. The main abdominal wound is closed with silk, taken through peritoneum and fascia for one layer and through the skin for a second. The animal is dressed with a catheter (#18-22 French) inserted in the pouch and held in position by several heavy silk sutures to the adjacent skin. For routine dressing, we spread a layer of vaseline around the stoma and over the surrounding skin. A heap of precipitated chalk (CaCO_3 , USP) is spread on top of this and is held down by a layer of vaseline-coated gauze and an outermost pad of cellucotton, 6 by 6 inches square. The entire dressing is supported by a towel, and a vest which binds it snugly against the abdomen and ties over the dog's back. A soft rubber catheter is inserted in the pouch if this is necessary to prevent closure of the stoma. We never use metal or plastic cannulas for gastric pouches of any kind, because of the possibility of irritation and trauma of the mucosal surface inside the viscus. Dressings are changed routinely one to three times a day, depending on the secretory activity when the dog is not being used for experiments.

CONVERSION OF A HEIDENHAIN TO A BICKEL-TYPE POUCH

Once the subcutaneous Heidenhain pouch has established a blood supply from the subcutaneous tissues, it is possible to divide the vascular pedicle without loss of viability. In our own experiments the conversion has not been done in less than six months, with one exception as noted above. Gregory and Ivy point out that, at the time of this second operation but prior to the division, one can obtain some indication of the adequacy of the blood supply derived from the subcutaneous vessels by intermittent occlusion of the vascular pedicle and observation of the color of the mucous membrane of the pouch stoma. Conversion is extremely simple. The previous midline incision is opened, and the vascular pedicle which runs from the spleen to the left anterior abdominal wall is divided between ligatures. In order to avoid subsequent adhesions between the omentum and the pouch, the peritoneum at the site of exit of the pedicle is closed over its stump with interrupted sutures. The main wound is then closed in layers as before.

ANTRECTOMY AND GASTRODUDENOSTOMY

In order to obtain a dog with a pouch in which the resting secretion contains no free acid 24 hours after the last meal, we have found it necessary to perform an extensive antral resection at the time of the first operation (6). After the pouch has been prepared, the left gastric vessel is divided at a point just proxi-

mal to the re-entrant angle; the right gastric artery and the vessels on the greater curvature are also divided. The antrum of the stomach is then removed, leaving a wide curved proximal opening in the corpus from which both the pouch and antrum had been excised. This opening is narrowed by partial closure of the lesser curvature portion of the cut end of the stomach (Hoffmeister procedure). An end-to-end anastomosis is performed between the remaining opening and the end of the duodenum (Billroth I). At times it is not feasible to do an end-to-end type of gastroduodenostomy; in these cases it is better to close the duodenal stump and make an end-to-side gastroduodenostomy just distal to this stump. The anastomosis is performed with interrupted sutures to avoid stenosis. A nonvagal pouch coupled with such an antrectomy of sufficient magnitude yields specimens of resting secretion with pH's almost invariably above 3.5 and usually above 7.0.

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RECENT EXPERIENCE WITH PERICARDITIS WITH SPECIAL REFERENCE TO IDIOPATHIC PERICARDITIS

STUART R. NEMSER, M.D., AND EPHRAIM DONOSO, M.D.

New York, N. Y.

INTRODUCTION

Past studies have shown that the leading causes of pericarditis are rheumatic fever, bacterial infection and tuberculosis (1). It appeared that over the last several years there had been a shift in the relative frequencies of the various etiologies of pericarditis. For this reason all cases of pericarditis seen over a two-year span were reviewed to determine the etiology, features leading to the diagnosis and responses to various therapeutic measures.

METHOD

All cases of pericarditis seen at The Mount Sinai Hospital during 1958 and 1959 were reviewed. It was decided to exclude from this series pericarditis secondary to thoracic surgery and the pericarditis occurring in the acute phase of myocardial infarction. Thirty-nine cases comprised this series.

THE SERIES AS A WHOLE

Of the thirty-nine cases of diverse etiology, twenty-one were male and eighteen were female. There were twenty-six white patients, eight Puerto Ricans and five Negroes. The ages ranged from five to seventy-one years.

The distribution of the various etiologies is given in Table I. Of interest is the finding that idiopathic pericarditis was seen far more frequently than any other of the listed forms of pericarditis.

A review of symptoms is indicated in Table II. To be noted is the disproportionately high incidence of a preceding respiratory infection, fever, and pain in the patients with idiopathic pericarditis.

Of the ten patients who were free of pain, two had acute rheumatic fever, two had myxedema, two had uremia, two had neoplastic involvement of the pericardium, one had chronic idiopathic pericardial effusion and another had an unclassified pericarditis.

The observed signs are shown in Table III. A pericardial friction rub was audible in slightly more than one-half the patients. Diagnosis of pericarditis in these cases was made on characteristic electrocardiographic and roentgenographic changes in conjunction with the clinical setting. Coexisting pneumonitis was found twice as frequently in the idiopathic pericarditis group.

An enlarged cardiac silhouette was present in 29 of 38 examinations (76%), while nine patients showed a normal cardiac shadow.

The electrocardiogram was abnormal in thirty-seven subjects (Table IV). Of

From the Division of Cardiology, Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

the two cases of idiopathic pericarditis with normal tracings, one was reported by the referring physician to have had ST segment elevations prior to admission; the other patient had some ST segment elevation in lead III with no subsequent changes. Three patients had abnormal cardiograms secondary to myocardial infarction (2) and rheumatic heart disease with mitral stenosis (1), but did not have any changes in their electrocardiograms when they had postmyocardial infarction and postcommissurotomy syndromes, respectively. Alterations in rate, rhythm and conduction included sinus bradycardia (three patients

TABLE I

Etiology of Pericarditis	No. of Cases
Idiopathic	19
Postmyocardial infarction syndrome	4
Neoplasia	4
Rheumatic fever	3
Myxedema	3
Uremia	2
Postcommissurotomy syndrome	1
Purulent	1
Chronic idiopathic pericardial effusion	1
Unclassified	1

TABLE II

Symptoms	Total Series		Idiopathic Cases		Miscellaneous Cases	
	No.	Per cent	No.	Per cent	No.	Per cent
Preceding upper respiratory infection . . .	23	59	18	95	5	25
Fever	28	72	17	89	11	55
Cough	16	41	8	42	8	40
Hemoptysis	3	8	1	5	2	10
Dyspnea	22	56	10	53	12	60
Pain	29	74	19	100	10	50

with myxedema), sinus tachycardia, atrial fibrillation, first degree heart block and right bundle branch block.

Thyroid studies were conducted on seven patients and proved the diagnosis of myxedema in three cases.

Tuberculin skin testing with PPD was carried out on twenty-three patients and was positive in thirteen. None of these patients had clinical tuberculosis.

Antistreptolysin O determinations were done in seventeen cases and were elevated (above 300) in six. Two of these were pericarditis occurring with active rheumatic fever and carditis. The other four were acute idiopathic pericarditis.

Treatment varied greatly, depending upon the etiology of the pericarditis. Corticosteroids were used in a total of fourteen cases; nine of idiopathic peri-

carditis, three of acute rheumatic fever and two of the postmyocardial infarction syndrome. There were excellent and prompt remissions of the symptoms in all such treated patients.

Four patients underwent operation for treatment and or diagnosis. A pericardiotomy was performed in a case of neoplastic involvement of the pericardium for relief of recurrent pericardial effusions that were causing cardiac compression. The patient with chronic idiopathic pericardial effusion had a pericardiectomy carried out for relief of cardiac compression and for histologic examination of the pericardium. This patient, recently reported by Scheuer, showed a

TABLE III

Signs	Total Series		Idiopathic Cases		Miscellaneous Cases	
	No.	Per cent	No.	Per cent	No.	Per cent
Pericardial rub	22	56	11	58	11	55
Pneumonitis	9	23	6	32	3	15
Pleural effusion	16	41	8	42	8	40
Right	2		0		2	
Left	6		3		3	
Bilateral	8		5		3	

TABLE IV

Electrocardiogram	Total Series	Idiopathic Cases	Miscellaneous Cases
Normal	2	2	0
Abnormal	37	17	20
Characteristic ST elevations	17	10	7
Nonspecific ST-T changes	14	7	7
Low voltage (accompanying)	5	2	3
Low voltage (only)	3	0	3
Unchanged	3		3

nonspecific subacute pericarditis on microscopic study with no evidence on culture or histology of tuberculous infection (2). Two other patients had open pericardial biopsies for diagnostic purposes. The pathologic reports were of a chronic nonspecific inflammation in one patient and a noncaseating granulomatous inflammation in the other. Both of these were regarded as idiopathic pericarditis.

Recurrences of pericarditis were not uncommon among the patients with idiopathic pericarditis and among those with the postmyocardial infarction syndrome. One patient with idiopathic pericarditis had at least five recurrences in less than a year.

There were ten deaths in this series with nine postmortem examinations. All four patients with neoplastic pericardial involvement died, as did both patients with pericarditis secondary to uremia. The patient who had pericarditis as part

of the postcommissurotomy syndrome recovered from that episode only to be readmitted and die of an acute yellow atrophy of the liver, possibly on the basis of serum hepatitis. There was one sudden and unexplained death in a patient who had recovered from a postmyocardial infarction syndrome and was asymptomatic. The patient with purulent pericarditis due to a staphylococcus died primarily from renal disease secondary to hypertension and diabetes mellitus. At postmortem examination this patient had 100 ml of purulent material in the pericardium with an acute endocarditis of the mitral valve, originating from a genitourinary infection. Another death was in a case of idiopathic pericarditis in which it was believed that anticoagulation resulted in hemopericardium and tamponade.

IDIOPATHIC PERICARDITIS

The leading cause of pericarditis as seen in this hospital (excluding from consideration pericarditis secondary to acute myocardial infarction or to thoracic surgery) now appears to be acute idiopathic pericarditis. Infectious pericarditis, pyogenic or tuberculous, which previously was the most frequent form of pericarditis is now rarely seen. Reeves found an incidence of ten per cent of idiopathic pericarditis in his series of 96 cases of acute pericarditis over the period from 1935 to 1950 (1). Sodemann and Smith reported on 240 cases of acute pericarditis collected from 1946 to 1956, in which there was an incidence of acute idiopathic pericarditis of 23 per cent (3). Idiopathic pericarditis comprised 49 per cent of our series studied in 1958-1959, with a variety of other types of pericarditis forming the remainder.

Of the nineteen patients with acute idiopathic pericarditis in this series, twelve were male and seven female, which is a lower male to female ratio than reported in most series (4-6). The racial incidence was thirteen white, three Puerto Rican and three Negro patients. The ages ranged from 16 to 66 with a mean of 41.9 years. Scherl (4) found a range of 22 to 73 years of age with a mean of 48.5 years in his series, while Krook found an age range of 16 to 84 with a mean of 37 years in his cases (7).

A history of a preceding upper or lower respiratory infection was obtained in eighteen of the patients (95%). Scherl (4) found such a history in 43 per cent of his cases while McCall and Hertz (5) described this in 89 per cent of their series.

Fever was present in seventeen cases (89%) in this series, in 83 per cent of Scherl's cases (4), and in all the cases in the series of McCall and Hertz (5) and of Chapman and Overholt (8). Cough was a prominent symptom in eight of our patients (42%) and hemoptysis was present in one (5%). Dyspnea, found in 37 per cent of Scherl's series (4) and in 41 per cent of Krook's cases (7), was present in ten patients in our series (53%).

Chest pain of a pleuropericardial nature was present in all nineteen cases. Since Chapman and Overholt (8) found chest pain in all their twenty patients and Scherl (4) in twenty-nine of his thirty subjects, a diagnosis of idiopathic pericarditis would appear to be most unlikely without this symptom. The pain

in our series was most frequently precordial or substernal and often radiated to the left shoulder and arm, neck, back and sometimes to the abdomen. Other authors (4, 7, 9) have remarked upon the confusion which may arise when the pain is substernal and radiates to the left arm, simulating the pain of acute myocardial infarction.

It was helpful in this series to consider in the differential diagnosis of the two conditions that the pain in pericarditis was sticking and sharp rather than squeezing; it was exaggerated by respiration so that the patient was often afraid to take a deep breath; it was frequently augmented by cough and motion of the trunk; and that it was very often ameliorated when the patient sat up and leaned forward.

The pain in one case in our series was predominantly epigastric and in two other patients there was radiation of the pain to the right and left upper quadrants of the abdomen, respectively. The diagnosis in the patient with right upper quadrant pain radiation was initially confused with acute cholecystitis. Powers *et al.*, have remarked upon the possible simulation of a surgical emergency when the pain is abdominal (10).

Of the physical findings, the most important and characteristic was a pericardial friction rub. A rub was heard at some time in the clinical course in eleven of the nineteen cases (58%). Other authors have reported an incidence of from 50 per cent to 100 per cent (4-6, 8). The rub may be to-and-fro or only systolic and may be evanescent or last several weeks. Most often the duration is about one week (4, 11). Since the rub may be very transient, a true incidence is difficult to determine and detection will depend often upon chance and frequency of auscultation. Gelfand and Goodkin encountered five patients with the classical clinical picture of acute idiopathic pericarditis with serial electrocardiographic changes, but in four of these patients a friction rub could not be heard at any time in their course (12).

Pneumonitis was found in six cases (32%) of this group. In two other series the incidences were 22 per cent and 50 per cent (5, 6). Pleural effusions were discovered in eight patients (42%) of this series, and all were on the left side or were bilateral in contradistinction to the pleural effusions seen in congestive heart failure which are usually right sided. This tendency has also been noted by others (4, 6).

Enlargement of the cardiac silhouette was found on thirteen of eighteen radiographic examinations (72%). Reports in the literature indicate an incidence ranging from 33 per cent to 70 per cent (4, 6, 8). The enlargement is due to the presence of pericardial effusion, although there may be some cardiac dilatation. At least 250 ml of fluid are necessary to cause a distinct change in the cardiac silhouette (11).

Many patients with acute idiopathic pericarditis showed evidence of some cardiac compression caused by the accumulation of fluid in the pericardium and the resulting increase in intrapericardial pressure. This manifested itself by pulsus paradoxus, dyspnea, rales, venous distention, and an enlarged liver, *i.e.*, as congestive heart failure. However, frank cardiac tamponade, an exag-

gerated and decompensated phase of cardiac compression suggesting shock, was present in only two instances. One patient necessitated emergency pericardiocentesis and the removal of 350 ml of fluid proved lifesaving. Another patient, in whom anticoagulants were given for presumptive pulmonary emboli, died after going into shock unresponsive to vasopressor therapy with concomitant disappearance of a pericardial friction rub. As postmortem examination revealed 500 ml of fresh blood in the pericardium, it is presumed that death occurred from acute hemopericardium and tamponade. In another series of thirty cases of acute idiopathic pericarditis there were no instances of tamponade (4).

Pericardiocentesis was performed in four cases. The fluid obtained was serous in two patients and serosanguinous in the other two, with the amount ranging from 125 ml to 1,000 ml. Pericardial effusion in idiopathic pericarditis has been noted to be sanguinous as often as it is serous. Fluid from taps early in the disease is usually serous in nature, while most of the sanguinous taps were obtained after fourteen days of illness (13).

Other reports indicate that from 40 per cent to 80 per cent of the cases of acute idiopathic pericarditis have a suggestive or typical electrocardiographic tracing (11). We found an abnormal record in seventeen of the nineteen patients (89%). Ten of these (52%) had characteristic ST segment elevations while seven (37%) had "nonspecific" ST-T changes. The ST segment elevations, probably caused by subepicardial myocarditis, were concave upward and showed no reciprocal depressions (except in AVR). These elevations can persist for one or two days to one or two weeks (4, 11). The T waves were seen to be concordant in the early stages and sometimes were increased in amplitude. Serial tracings showed that as the ST segment returned to the baseline, the T wave became flattened, diphasic, and then inverted. The last observed change was a return of the T wave toward the upright position. The T wave inversions may last several months (11). Arrhythmias and heart block are said to be uncommon (11); in our series one patient had a prolonged PR interval (first degree heart block) and another had an incomplete right bundle branch block.

The white blood count is elevated in most cases, usually in the range of 10,000 to 20,000 per cu mm. In our series 78 per cent of the determinations fell into this range, while in another study (4) 50 per cent of the patients had a leukocytosis, generally between 10,000 and 15,000. There is usually both a relative and absolute increase in the polymorphonuclear count.

A rapid erythrocyte sedimentation rate was found to be uniform, being present in all nineteen patients and being greater than 100 mm per hour in nine (47%). Chapman and Overholt (8) found an increased sedimentation rate in all of their twenty cases, McCall and Hertz (5) in all of their eighteen cases, and Reid *et al.* (6) in sixteen of their twenty cases.

The serum glutamic oxaloacetic transaminase was found to be elevated in two patients (57 units and 92 units). Nydick *et al.* found no alterations of the transaminase activity during the acute phase of pericarditis in nine of eleven cases (14). Of the two of his patients who had minor transaminase elevations, one had definite liver function abnormalities and the other had advanced mye-

ogenous leukemia with marked hepatosplenomegaly. Kalmansohn and Kalmansohn found elevated transaminase levels in six of seven consecutive patients with pericarditis (15). In four of these cases the maximal level was below 75 units, but in two patients the levels exceeded 100 units and were within the range seen in patients with transmural myocardial infarction. These authors concluded that the serum transaminase is of value only in the differentiation of pericarditis and myocardial infarction when the levels are within normal limits.

The lupus erythematosus preparations were negative in all cases examined. The similarities and differences between the pericarditis of disseminated lupus erythematosus and that of the acute idiopathic form have been reviewed recently (16).

Titers of antistreptolysin O were found to be elevated in four cases of idiopathic pericarditis and ranged from 333 to greater than 1250 units. It was interpreted in this study as indicating a recent streptococcal infection and in one case only was there confusion with the pericarditis of acute rheumatic fever. Rheumatic fever with pericarditis usually presents a different clinical picture from acute idiopathic pericarditis and it carries a more adverse prognosis.

A tuberculin skin test using purified derivative (PPD) was done on fifteen subjects and was positive in ten. As Stepman and Owyang (17) found a positive tuberculin test in sixteen of seventeen cases of tuberculous pericarditis, a negative test would be helpful in excluding tuberculosis as the cause of the pericarditis. This exclusion would make it unnecessary to "cover" a patient with antituberculous drugs when corticosteroid therapy is instituted for idiopathic pericarditis. In our series, of the ten patients with idiopathic pericarditis and a positive PPD, six received treatment with steroids and five of these patients were "covered" with antituberculous drugs. Whether such therapy is necessary in patients with a positive skin test is moot. The beneficial effect of steroids on acute idiopathic pericarditis is usually apparent within a few days, often within twenty-four hours, and the risk of spread of tuberculosis within that time is doubtful. We have had no experience with the response of clinically primary tuberculous pericarditis to steroids and know of no reports indicating that a response similar to that in idiopathic pericarditis occurs. The decision whether or not to use antituberculous drugs concomitantly with steroids in cases of idiopathic pericarditis with positive tuberculin skin tests will rest on clinical judgment based on the presenting features and experience with tuberculous pericarditis in the particular area and population. In this hospital tuberculous pericarditis has been rare, whereas Schrire dealing with a predominantly colored and Bantu population in South Africa found tuberculosis to be the definite or probable etiology in 75 per cent of his 160 cases of pericarditis (18).

Viral studies in the form of serum titers were done in fourteen of the nineteen cases. These studies included heterophile antibodies, cold agglutinins and streptococcal MG agglutinins, and antibodies to Cocksackie, influenza, and adenopharyngoconjunctival viruses. A significantly elevated neutralizing antibody titer to a Cocksackie virus Group B, Type 4, in one case could not be adequately

evaluated as no comparison between acute and convalescent sera was available. That Coxsackie viruses can cause pericarditis has been shown (19) and it is thought that these viruses may be the etiologic agents in certain cases of acute idiopathic pericarditis. Of the cases of acute pericarditis associated with Coxsackie virus infection reported in the literature, most occurred in male patients and the great majority were associated with Coxsackie Group B, Type 5 virus (20, 21).

There was a prompt response of the symptoms in the patients with acute idiopathic pericarditis who were treated with corticosteroids in comparison to those who were treated with salicylates or who received no therapy. The improvement after institution of steroid therapy was usually within twenty-four to forty-eight hours and sometimes after one or two doses in the range of 15 mg of prednisone. However, the frequent finding of combinations of therapy and the relatively small size of the group require that this impression of dramatic response to steroid therapy be confirmed by additional investigations. Five patients received no therapy exclusive of bed rest, two received only salicylates, and two were given only antibiotics. In the steroid treatment group, three patients were given steroids as the sole therapeutic agent, one patient received both steroids and salicylates, and five had steroids as well as antibiotics. An additional patient received various regimens at different times in his hospital course.

According to Spodick, the average duration of illness in acute idiopathic pericarditis is two weeks with recurrences in one patient in seven (11). Scherl (4) found a recurrence rate of 36 per cent, while we found recurrences in seven of nineteen patients (37%). One patient had five recurrences in less than one year, another had three recurrences over a two-year period, and the other five had one recurrence each. The recurrences often followed the tapering or the cessation of steroid therapy, and for no discernible reason.

The signs, symptoms, tendency toward recurrences, and response to corticosteroid therapy that are seen in acute idiopathic pericarditis are similar to those occurring in two other pleuropericardial syndromes, *i.e.*, the postcommissurotomy syndrome and the postmyocardial infarction syndrome; however, these conditions should not be a problem in the differential diagnosis of idiopathic pericarditis. The postcommissurotomy syndrome follows mitral valvulotomy in from 10 per cent to 63 per cent of cases, usually ten days to two months after operation (22). Since an identical syndrome is seen in patients who have undergone cardiac surgery for heart disease other than rheumatic, as in congenital heart disease (23, 24), it would seem preferable to describe this entity under the name of postpericardiotomy syndrome. The postmyocardial infarction syndrome, first described by Dressler in 1956 (25) and recently reviewed by Weiser *et al.* (26), is probably often overlooked and ascribed to extension of the infarction, pulmonary embolism, and congestive heart failure.

Acute idiopathic pericarditis has also been called acute benign pericarditis and benign idiopathic pericarditis; however, the benign nature of this entity has been questioned. Reports of fatal cases, although rare, have been published.

Price *et al.* reported a case of idiopathic pericarditis in which there was sudden death during renal insufficiency (13). At postmortem examination there were 1,000 ml of blood-stained pericardial fluid; however, the authors thought that although tamponade could have accounted for the death, the blood pressure had been adequate immediately prior to the patient's demise and that the cause of death was unknown. They cited four previous reports of fatalities, two of which occurred suddenly, and re-emphasized that death has occurred quickly in acute idiopathic pericarditis and that the amount of pericardial fluid found at postmortem may be insufficient to have caused cardiac embarrassment. Roman *et al.* recently reported another fatal case in which the pericardial sac contained 150 ml of bloody fluid, but in which tamponade was considered unlikely (9). The fatal case in our series was attributed to hemopericardium and tamponade.

In addition, there are reports indicating that acute idiopathic pericarditis can lead to a subsequent fibrous pericardium (27) and to chronic constrictive pericarditis (7, 28). It is conjectural whether the case of chronic idiopathic pericardial effusion in this series had a previous acute idiopathic pericarditis, and whether this represents a transitional stage toward the development of a constrictive pericarditis.

SUMMARY

Review of the cases of pericarditis seen in a general hospital over a two-year span has shown that acute idiopathic pericarditis is the leading cause. Features of this form of pericarditis are presented and compared to those found in the forms of pericarditis secondary to known etiologies and to those of idiopathic pericarditis found in the literature. The response in the patients with acute idiopathic pericarditis to adrenocorticosteroids was impressive and should be further confirmed by others.

ACKNOWLEDGMENT

We wish to thank Dr. Charles K. Friedberg for his advice and encouragement.

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Clinico-Pathological Conference

DIARRHEA, ANEMIA AND SEVERE CHOLESTATIC JAUNDICE

Edited by

FENTON SCHAFFNER, M.D.

New York, N. Y.

A 24 year old white unmarried female of Italian descent was admitted to The Mount Sinai Hospital because of massive rectal bleeding for one day.

She was well until 9 years of age except for some cough and wheezing since an attack of pertussis at 4. She had abdominal pains and 9 months later, bloody diarrhea with fever. Anemia and ulcerated areas throughout the rectosigmoid were found at a local hospital. Results of hepatic tests were normal. She was given two blood transfusions. Three months following the transfusion, she became jaundiced and was admitted to Babies Hospital. At this time the liver edge was felt 2 cm below the right costal margin and the spleen 4-5 cm below the left costal margin. These were not noted before. Hemoglobin was 8.6 Gm% with hypochromia, polychromia and stippling seen on smear. Reticulocyte count was 6%. See table (1946). Chest x-rays showed increased bronchovascular markings on the right and barium enema showed an area of narrowing in the distal sigmoid. Results of all other studies were normal. The jaundice faded and all the symptoms gradually disappeared although on discharge cephaline flocculation was still 2+ and BSP retention 25%.

A year and a half later she was seen at the Lahey Clinic because of persistent fever, diarrhea and weight loss. Physical examination was negative. Hemoglobin was 11.6 Gm% and the white count was normal. See table (1948). Sigmoidoscopy showed only friability of the mucosa. X-rays of the chest and gastrointestinal tract were normal although the gallbladder failed to visualize. Fever and bloody diarrhea persisted and a year later she was admitted to the Grace-New Haven Community Hospital at the age of 13. Prior to this admission the enlarged liver and spleen were again noted and her diarrhea became severe. Her skin was brownish-yellow but the sclerae were not icteric and the liver and spleen were both down 2-3 fingerbreadths. No other abnormal physical findings were noted. A blood smear revealed target cells and red cell fragments with slightly decreased fragility. See table (1949). X-rays of the skull and hands were normal and the gallbladder again failed to visualize.

One year later she began menstruating and over the next five years she had six scanty periods. At the age of 14 a colectomy was recommended because of diarrhea but then the patient began to improve gradually. For four years she was relatively well with intermittent diarrhea only until the age of 18 when she was

From the Department of Pathology, The Mount Sinai Hospital, New York, N. Y.

admitted to Johns Hopkins Hospital because of fever and diarrhea following two months of sore throat and aphthous stomatitis. The only abnormalities found on physical examination were the liver edge down one fingerbreadth, a barely palpable spleen tip and healing small ulcers around the ankles which the patient said had been "coming and going" during the past few years. Hemoglobin was 11.4 Gm% with 5 million red cells mm^3 . Hypochromia, anisochromia, anisocytosis, stippling, nucleated and target cells and poikilocytosis were noted. White count was normal. Several stools were guaiac positive. See table (1954). Serum electrolytes, blood NPN and sugar and thyroid function were normal. X-rays showed only a large spleen. In the hospital she developed urticaria following penicillin and allergic conjunctivitis after Azulfidine. All symptoms gradually subsided on symptomatic therapy as they had in the past. Two years later she was admitted to the Hospital of The Rockefeller Institute for study of her hematologic problem. Anemia and splenomegaly were found in her father and in several members of his family, and hay fever and asthma were common on both sides of the family. X-rays of the chest and esophagus were normal. See table (1956).

One year later the patient was admitted to a local hospital because of right lower quadrant pain and continuing diarrhea up to 15 bowel movements a day. On examination a slightly enlarged thyroid and a slightly enlarged liver were found with diffuse lower abdominal tenderness. X-rays of the colon revealed a tubular appearance with some serration of the edges. She was given steroids as in the past, but without relief. Because of ankle edema, she was given Diamox.

She was admitted to The Mount Sinai Hospital at age 22 for the first time to attempt to control the diarrhea. On examination the only abnormalities were nontender hepatosplenomegaly of 2 to 3 fingerbreadths. Repeated urinalyses showed occasional traces of albumin and bile, urobilinogen to 1:80, and occasional red and white cells. Hemoglobin was 8.9–10.1 Gm%. White blood counts and differential counts were normal. Target cells were prominent and 3% reticulocytosis was found. Sedimentation rate was 35 mm. hr. Blood sugar and BUN were normal. See table (1958). Tuberculin test and serology were negative. Hemoglobin was all type A with 3.6% alkali resistant. Bleeding and clotting times and clot retraction were normal. Serum electrophoresis showed only a diffuse increase in gamma globulin. A liver biopsy was performed. X-rays of the chest, bones and upper gastrointestinal tract were normal. Cholecystogram and I.V. cholangiogram failed to visualize the gallbladder or bile ducts. Barium enema revealed complete loss of haustral markings with shortening of the colon. The terminal ileum was normal. No abnormal elements were found in a duodenal aspirate on a secretin test but a nonfunctioning gallbladder was suspected.

In the hospital the patient continued to have diarrhea and some ankle edema although she was afebrile. She had several attacks of wheezing, especially after she was given cholecystokinin; they responded to Benadryl. She was discharged on chlorothiazide and symptomatic therapy. Shortly after discharge, she had a perirectal abscess which spontaneously opened and drained.

During the next two years she became more jaundiced and the spleen enlarged

although the other symptoms remained unchanged except for frequent respiratory infections and attacks of wheezing. See table (1959). Just before her 24th birthday, she became very jaundiced and ascites developed which responded to salt restriction and Diuril. Her diarrhea increased in frequency to 20 water bowel movements a day and after two weeks there was sudden massive rectal bleeding which brought her to The Mount Sinai Hospital for the last time.

On examination she was deeply icteric, had a fetor hepaticus, temperature 100°, blood pressure 90/60 and pulse 120/min. Flapping tremor, spider nevi and palmar erythema were absent. The liver and spleen were down two finger-breadths. Both were smooth, firm and nontender. No definite ascites was present

TABLE I
Results of Liver Function Tests

	1946	1948	1949	1954	1956	1958	1959	1960	
								Admission	Terminally
Bilirubin, mg% total/conjugated	2.9/1.4	—	—	3.2/2.0	sl. up	3.4/1.7	9.0/5.8	37/25	96/62
Cephalin flocculation	2+	1+	2+	3+	—	1+	2+	2+	2+
Thymol turbidity, u.	—	4.5	8.5	7.2	—	2.6	—	—	—
Albumin/globulin, Gm%	3.4/3.7	—	—	4.1/3.6	—	3.5/3.9	2.6/5.2	3.0/3.9	3.1/2.8
Cholesterol, mg% total/esters	105/47	—	—	265	—	210/156	330	—	—
Alkaline phosphatase, u.	6.1 B	—	30 B	39.3 B	—	84 KA	90 KA	42.6 KA	89 KA
BSP % retention	50	15	—	—	26	40	—	—	—
Prothrombin time, seconds	55	—	—	21	—	12.5	—	14	—
SGOT, u.	—	—	—	—	—	73	78	—	—

but slight ankle edema was found. The rectum was tight and tender and much perirectal fibrosis was felt. Gastric aspirates were guaiac negative. Urinalysis showed traces of albumin and sugar, 3+ bile and many white cells. Hemoglobin was 11 Gm% and the white blood count 20,800 with a shift to the left. Target cells and reticulocytes were numerous. Platelets were normal. Serum electrolytes were normal. See table (1960). X-rays of the abdomen showed no dilatation of the colon. The patient was given blood, ACTH, penicillin and streptomycin but as the bleeding was not controlled, a subtotal colectomy and ileostomy was performed. The colon was grossly very inflamed, the spleen was football-sized and the liver was not enlarged but grossly nodular. Many distended veins were present in the upper abdomen and retroperitoneal nodes were enlarged and succulent.

Postoperatively, the patient gradually improved for a week when she again began to bleed from the rectal stump. However, it was felt that the drop in

hemoglobin was greater than could be explained by blood loss. The serum bilirubin began to rise spectacularly and at the end of the second postoperative week, rectal bleeding again became massive, necessitating resection of the remainder of the rectum. Following this operation she was oliguric, dyspneic and hematemesis developed. Despite pressor amines, vitamin K, blood, fresh frozen plasma and esophageal tamponade, the patient expired 5 days after the second operation, 19 days after the first, and 15 years after the onset of symptoms.

*Dr. Alexander B. Gutman**: This was an unusual and complicated case because this young woman, age 24, had not one but several diseases, both discrete and interrelated. One of these I take to be ulcerative colitis, which pursued a relentless course until her death. Another I am going to interpret as thalassemia with complications that relate to the picture as a whole. She was sensitive to a variety of drugs and had bronchial asthma, so she had hypersensitivity. Finally, all of these diseases seemed to converge upon the liver, and she had a very interesting disorder of that organ. I dare say that hardly any organ in her body was unaffected, and it is precisely this kind of situation which brings a gleam to the eye of the pathologist and a slight tremor to the clinician who discusses the case.

Instead of going through the entire history chronologically, I would like to pick out each of the disorders in question and trace them through.

We will begin with the ulcerative colitis, which was her most serious disorder and ultimately caused her demise. This disease began at age 9 with abdominal pains followed by bloody diarrhea. Sigmoidoscopy revealed ulcerations in the rectum and sigmoid, and apparently these were quite typical. At that time she presented anemia, which I think was interpreted as due to blood loss through the bowel. She had a remission, spontaneous or induced, but a year and a half later there was a recurrence, again with fever and diarrhea. By the age of 14 her symptoms were severe enough to suggest colectomy but again there was a remission which persisted for four years except for intermittent diarrhea. At age 18 there was a severe recurrence of symptoms, chiefly diarrhea, fever and bleeding through the bowel, with anemia. The subsequent remission was of short duration. The following year there was again an exacerbation, this time with rather severe pain in the right lower quadrant and diarrhea. X-rays at this juncture revealed a tubular appearance of the colon due apparently to loss of haustral markings. She was admitted to this hospital for the first time at the age of 22, again because of diarrhea. Soon thereafter she had a typical complication of ulcerative colitis, namely, a perianal abscess, which drained spontaneously. At the age of 24 she had massive rectal bleeding which necessitated immediate hospitalization. A trial of corticosteroids and ACTH, supported by a variety of antibiotics, was to no avail. The profuse bleeding continued and, in spite of the severe jaundice then present, a subtotal colectomy and ileostomy was performed. She recovered from the extensive surgical procedure, but rectal bleeding soon recurred, so that the rectal stump, in desperation, had to be resected. Five days later the patient succumbed, 15 years from the date of onset of ulcerative colitis.

* Director, Department of Medicine, The Mount Sinai Hospital, New York.

While all this was going on, this young Italian girl was suffering concomitantly from a blood dyscrasia, which throughout was aggravated and somewhat distorted by the loss of blood from the gut, at times very manifest, at other times occult. In going over the history and trying to follow the thread of disease, it is difficult to dissociate the two causes of anemia. At age 9, it was noted that the spleen extended 4 to 5 cm below the costal margin, a rather marked enlargement in respect to the rectal bleeding even though this was extensive. The hemoglobin was 8.6 Gm%. Peripheral blood smear showed hypochromia, polychromia and rather marked stippling, which persisted throughout the course, and 6 per cent reticulocytes. Later, characteristic target cells were noted in the smear. At age 14 the blood smear again showed a rather marked anemia with striking abnormalities in the morphology of the red blood cells: hypochromia, anisocytosis, marked stippling, poikilocytosis and many nucleated and target cells. Throughout the course, the leukocytes were entirely normal; no malignant forms and no lymphadenopathy were noted. At age 14, five years after the spleen was found to be very large, the spleen tip was barely palpable, although x-ray did show an enlarged spleen. One wonders whether she had suffered splenic infarcts in the interim. There were recurring ulcerations of the skin about the ankles as one sees in certain types of hemolytic and related anemias. Finally, at the age of 16, other members of this family were examined, and anemia and splenomegaly were found in the father and in several members of the family. Apparently the maternal branch showed no abnormalities of the blood. Six years later when her hemoglobin was 9 to 10 Gm%, there were again many target cells in the peripheral smear, with 3 per cent reticulocytes. At this time we have some data on the chromatographic separation of hemoglobin. It was found to be all type A, and only 3.6 per cent was alkali resistant. The consistently pronounced anemia and splenomegaly which, to be sure, did vary, with characteristic erythrocytic abnormalities in a young Italian female who had a family background of anemia and splenomegaly, suggests thalassemia. Survival was too protracted, particularly in the face of the other disabling diseases, for the homozygous state. No mention is made of mongoloid characteristics. The x-rays of the skeleton failed to show any expansion of the marrow in the skull or long bones. There was very little F hemoglobin. So I think we would not be justified in calling this thalassemia major, but more properly an intermediate or minor form of this inborn defect. The stippling and target cells cannot be attributed to lead poisoning; nor does the picture suggest any of the so-called pseudothalassemias due to pyridoxine deficiency or the male-sex-linked syndrome which is sometimes called pseudothalassemia. Whether or not there was a combined C or E hemoglobinopathy cannot be deduced from the evidence at hand, and I am not sufficiently familiar with the clinical picture to make any guess without more specific data.

I should mention in passing that an occasional complication of thalassemia is cholesterosis of the gallbladder and cholesterol cholelithiasis. The gallbladder was not visualized on repeated attempts, but the dye was given when the patient was frankly jaundiced and presumably had overt liver disease which might well account for the failure of the dye to concentrate in the gallbladder. On one occa-

sion, apparently, cholesterol crystals were found in the duodenal aspirate, and I shall assume that she did, in fact, have involvement of the distal biliary tract.

All of this converges upon the liver in a way that I will try to point out. We will now consider what might have occurred in her liver. We know from the operative findings on her final hospitalization, when she was 24 years old, that she had a cirrhosis of the liver, since it is described as grossly nodular, although not enlarged, and there was portal hypertension as indicated by numerous distended collaterals and a spleen which was grossly enlarged, at least in part attributable to portal hypertension.

There are some unusual features, however, about this cirrhosis or at least about the tests of liver function that were made. At the age of 10 she was not markedly jaundiced but she had a 2+ cephalin flocculation test. I must warn you about the interpretation of this test under these circumstances because Dr. Hanger found that certain forms of hemolytic anemia were likely to be associated with moderately positive reactions. The result in this patient therefore might not be due to intrinsic liver disease but a reflection of certain phases of a hemolytic anemia. There was no gross hyperglobulinemia. The serum albumin was normal. However, the serum cholesterol was low at this point, and there was 50 per cent BSP retention with an increase of prothrombin to 55 seconds. Therefore, severe damage to the liver parenchyma was present despite the slight degree of jaundice.

Two years later the significant finding was a reduction in the BSP retention to 15 per cent. Apparently she was not jaundiced, as no serum bilirubin determination was made.

Next year we come upon an item which is of interest because it persists throughout her course, namely, increased serum alkaline phosphatase activity to 30 Bodansky units. Even taking into account that this is a growing child, this is a rather unexpectedly high serum alkaline phosphatase, which I do not think we can explain either on the basis of growth or of skeletal changes related to her hemolytic anemia because x-rays failed to show any. She had persistently and strikingly elevated serum alkaline phosphatase levels two years before death, and these require some explanation. The serum cholesterol showed a tendency to rise, reaching 330 mg% which is rather high for a young female with a hemolytic disorder. The serum albumin tended to fall; the serum globulin to rise. Unfortunately, these figures are difficult to interpret because she had many perianal abscesses related to her ulcerative colitis, which might have contributed to the hyperglobulinemia. Until two years before death she had no significant hyperglobulinemia. This would be very unusual for a girl who had postnecrotic cirrhosis of the type that Bearn emphasized; such patients tend to have extraordinarily high levels of serum globulin (1). In our patient the serum globulin finally decreased. This may be because the underlying infection declined or it may have been a terminal drop in serum globulin formation.

Of interest also are the serum bilirubin levels which preoperatively reached 37.6 mg% of which 24 mg% was conjugated, leaving a sizable fraction of unconjugated bilirubin. Just prior to death, the serum bilirubin levels were astronomical, allegedly 96 mg% total bilirubin, of which 62 mg% was conjugated, again a

very large amount of unconjugated pigment which we can explain only by assuming that she had increased production of bilirubin as a result of her hemolytic process and difficulty both in conjugating and excreting it.

The main thing we have to explain, however, is the prominent biliary obstructive element in this patient's liver. I will list some possibilities and indicate my preference. First is that she did indeed have postnecrotic cirrhosis, developing presumably from the serum-transmitted hepatitis at the age of 9, and perhaps at the age of 24 a hepatoma or multiple hepatomas developed which might have had an obstructive effect on the intrahepatic biliary tract. We have very little to indicate postnecrotic cirrhosis of this severity progressing over this number of years. I think the serum alkaline phosphatase levels are too high for this explanation.

Secondly, we might be dealing with a complication of ulcerative colitis which would be responsible for the obstructive element. This might take the form of a fatty liver or fatty cirrhosis which one sees associated with malnutrition in ulcerative colitis. We might consider the possibility of pseudopolyposis related to ulcerative colitis, with carcinomatous degeneration and metastases to the liver. Also, amyloidosis is by no means a rare complication of ulcerative colitis, and might cause enlargement of the liver and spleen with a rise in serum alkaline phosphatase. Pylephlebitis with liver abscess is possible. One or another of the many drugs that she took to control her ulcerative colitis could have affected her. We know that she had exquisite drug hypersensitivity which might have elicited intrahepatic cholestasis, but the evidence of biliary tract obstruction persisted for so many years that it seems unlikely that any such cause could be at the bottom of her difficulties.

The obstructive picture might conceivably have been the result of a complication of thalassemia. In thalassemia one does not see very marked hemosiderosis or secondary hemochromatosis because thalassemia is not exclusively a hemolytic disorder but rather is associated with difficulty in the generation of red cells or hemoglobin in the earlier phases of erythropoiesis.

Finally, and this is the explanation I am going to favor, she might have had obstruction of the extrahepatic biliary tract due to cholesterol stones in the common bile duct and in the gallbladder. I hasten to add that at no time is there any indication of complete obstruction of the extrahepatic biliary tract. The stools were never clay-colored, but partial obstruction might have occurred rather early in life, which would account for the persistence of the obstructive element for so many years. I am going to suggest that while I expect the findings in the liver to be multiple, there will be a large element of chronic obstruction of the biliary tract, principally a form of biliary cirrhosis.

*Dr. Hans Popper**: Thank you very much for an excellent analysis of what is obviously a very difficult case.

As the record states, a liver biopsy was obtained in 1958, two years before the

* Pathologist-in-Chief, The Mount Sinai Hospital, New York.

death of this patient. I think we should see what can be read in the liver biopsy specimen.

Beginning cirrhosis formation with some suggestion of a developing nodule was seen. The liver cells looked annoyingly normal. There was some mobilization of the Kupffer cells and bile stasis. At that time the serum bilirubin was in the range of 2 mg%. Electron microscopic study of the specimen was even more annoying because the endoplasmic reticulum of the liver cells was well preserved and the mitochondria looked quite normal. The only abnormal finding recorded in the electron micrograph was dilatation of bile canaliculi with alteration of

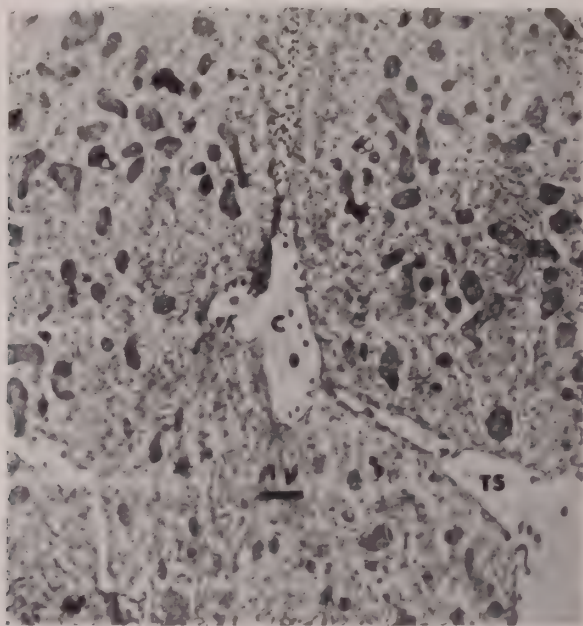


FIG. 1. Electron micrograph of liver biopsy specimen showing dilated bile canaliculus (c) near tissue space (TS). This cytoplasm appears normal. ($\times 6,000$)

the microvilli (Fig. 1). This was evidence of cholestasis of whatever cause without any significant hepatocellular injury. Returning to the more conventional microscopy, we saw no microcollapse or evidence that liver cells had been lost. Fibrosis was present in the portal tract with distinct scarring and bile duct proliferation. On closer inspection the bile ductules looked very mature. They were not the rapidly proliferating bile ductules of cholangitis. Fibrosis with fibroblasts was present around the bile ductules. In other areas where there was a little more bile ductular proliferation, immature bile ductules surrounded by segmented leukocytes were present.

The diagnosis was beginning cirrhotic transformation with portal inflammation and scarring, slight cholestasis and very little liver cell injury.

Immature bile ductules rapidly proliferating are seen more in the intrahepatic cholestasis while in extrahepatic obstruction we see scarring with fibroblasts,

mature bile ductules and segmented leukocytes. Therefore, the biopsy findings were very confusing. We had to wait to see what had happened until two years later when the young lady was then examined at autopsy.

First, in the surgical specimen of the colon obtained 17 days before death, significant ulcers were seen with thickening of the submucosa, a typical picture of ulcerative colitis (Fig. 2). Ulcerative colitis may be subdivided into three forms: 1) the form where the mucosa is altered and microabscesses form, which we did not see here; 2) the form with vascular involvement (the arteries in the present case were quite normal but there was some venous involvement); and

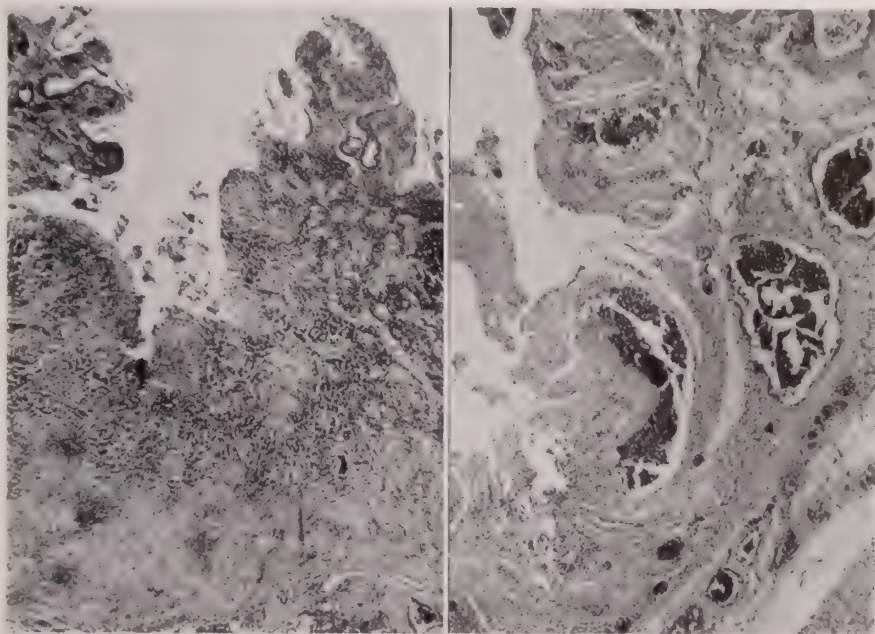


FIG. 2. Ulcers extending into submucosa in surgical specimen of colon with ulcerative colitis. (H & E $\times 63$)

FIG. 3. Eroded esophageal varices. (H & E $\times 63$)

3) classical nonspecific ulcerative colitis as seen here with marked infiltration in the submucosa of lymphoid elements and plasma cells. This suggests immunologically induced injury, and the lymphocyte-plasma cell combinations have been designated as immunologically competent cells, although we really have no idea how these cells are immunologically competent.

Pseudopolyps were present and some believe that they may be related to cancer, but here there was no cancer. This relation is still quite debatable. In some areas there were some attempts at healing. In this type of ulcerative colitis, there is involvement of the small intestine, and indeed the small intestine in this case showed thickening and swelling of the terminal ileum. A fairly acute ileitis was present with a large amount of infiltrating lymphocytes and plasma cells.

At the autopsy there was little colon left. The stomach was full of blood from erosions. In addition esophageal varices were eroded and bleeding (Fig. 3). The patient died from gastrointestinal hemorrhage with a nonspecific shock reaction secondary to the lower gastrointestinal tract disease.

The kidney showed the green discoloration of icteric nephrosis, which one would expect with a conjugated serum bilirubin level of over 60 mg%, supporting the accuracy of laboratory findings, if nothing else. Blood had accumulated at the cortico-medullary junction, the characteristic shock picture, again to be expected from the clinical history. Small atelectic and occasionally hemorrhagic foci found in the lung belong to the same group of shock lesions.

The spleen weighed 850 grams. On the cut surface, it had a meaty appearance. On histologic examination there was a considerable amount of blood in the spleen. Several features were noted: the red cells showed targeting; reticulo-endothelial proliferation of a severe degree was present, as expected under the circumstances; extensive fibrosis with pseudogland formation was noted which was a reflection of the portal hypertension.

The liver weighed 2,000 grams. It had some cirrhotic features with a significant degree of septal formation and nodularity. The extrahepatic biliary tract was normal from the papilla to the bifurcation of the hepatic duct including the gallbladder. There was neither a stone nor a stricture. The architecture of the liver was distorted but it was not the picture of postnecrotic cirrhosis. There were no big nodules although cirrhotic transformation surely was present. Some regenerative nodules and some septa connecting portal and central canals were found, but not too many (Fig. 4). Normal central veins were also seen which occur in postnecrotic cirrhosis, but there was not enough to call it postnecrotic cirrhosis, so we had to say only that some cirrhotic features were present (Fig. 5). Centrolobular necrosis, on an ischemic basis, occurred as a terminal event in a patient who was bleeding and who was operated on twice (Fig. 6). In the centrolobular area, particularly where there was no necrosis, classical bile stasis was present, as expected. There were a few iron granules in occasional Kupffer cells, in view of the thalassemia, but hemosiderosis was not present.

The liver cells away from the central zone in a woman dying with an astromic bilirubin level were again normal. Hepatocellular injury was not a prominent feature. The bile stasis was focally present throughout the liver. The most severe bile stasis was around portal tracts with feathery degeneration, microcalculi and proliferating bile ductules. There were some areas of markedly accentuated bile stasis with destruction of liver cells, but away from these areas the liver cells looked quite normal. However, a feature was noted which we often see as a result of the areas of focal bile stasis, namely, a connective tissue barrier separating the parenchyma from the portal tract, as in biliary cirrhosis. We have to assume that a peculiar biliary cirrhosis was present, but focally accentuated bile stasis does not fit. Also, as in biliary cirrhosis, we saw lymphoid accumulation which is either primary or secondary.

In the absence of extrahepatic biliary obstruction, we found features which

we like to associate with extrahepatic biliary obstruction. We saw classical bile infarcts in which bile-laden liver cells were so severely damaged as to become necrotic (Fig. 7). Some mechanical factor must have been operative because bile extravasates from bile ducts were present. Therefore, in what seemed to be a primary biliary cirrhosis, signs of extrahepatic biliary obstruction were seen. This would be secondary biliary cirrhosis. The patient clearly had secondary biliary cirrhosis mechanically produced, but due to what? In the portal tract, the most distinct scarring was around the bile ducts. There was a severe sclerosing cholangitis with virtual obstruction and obliteration of the lumens of middle-

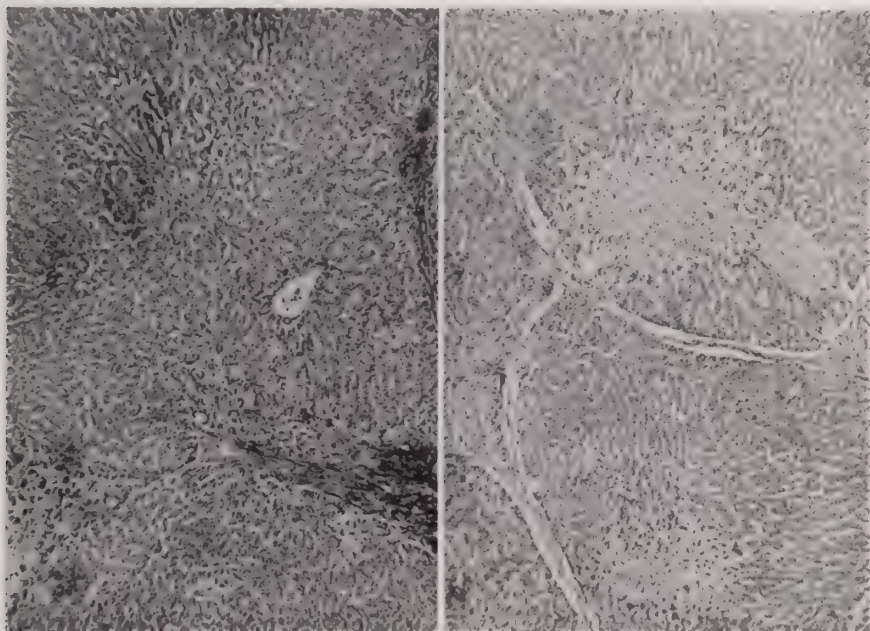


FIG. 4. Section of liver with septa dissecting the lobular parenchyma and intact central veins. (Chromotrope aniline blue $\times 63$)

FIG. 5. Centrolobular ischemic necrosis in liver. (H & E $\times 63$)

sized bile ducts in some areas. The large bile ducts were free. The smaller bile ducts were also obstructed and squeezed by the sclerosing tissue. This sclerosing cholangitis led in some areas to secondary biliary cirrhosis, but in most areas the lesion was only sclerosing intrahepatic cholangitis. Around areas of the sclerosing cholangitis there was tremendous proliferation of the adnexal glands (Fig. 8). They were rather bizarre looking but not carcinomatous (2). It was not a completely incidental finding that there was this irritation of all the glands. Material from the bile appeared pressed into the lymphatics, possibly in part explaining the high serum bilirubin level.

Let us try to put the entire lesion together. The diagnosis was sclerosing intrahepatic cholangitis with progressive, focally accentuated, biliary obstruction, leading to hydrohepatosis, bile extravasation and bile infarction, resulting in

classical secondary biliary cirrhosis, but not secondary to extrahepatic obstruction but to intrahepatic sclerosing cholangitis.

Linking of portal tracts with central canals by septa carrying vascular shunts accounted for the ischemic necrosis in the presence of a hemorrhage and in part for the portal hypertension. There were occasional regenerative nodules which accounted even more so for the portal hypertension reflected in the esophageal varices and splenomegaly. The splenomegaly was also produced by the thalassemia minor. Portal tracts had sharp borders, focal destruction of bile ductules and lymphoid accumulation which were barriers separating the biliary

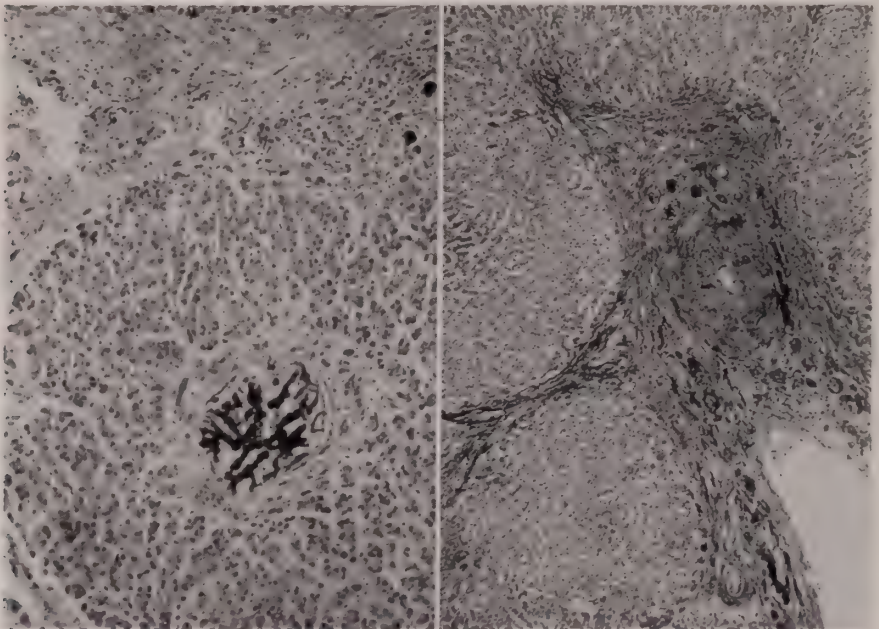


FIG. 6. Extravasation of bile in hepatic parenchyma producing bile infarct. (H & E $\times 120$)

FIG. 7. Severe scarring around medium-sized intrahepatic bile ducts with narrowing of the lumen. (Chromotrope aniline blue $\times 63$)

tree from the parenchyma, which is so characteristic of biliary cirrhosis. Liver cell damage was present only where cholestasis was severe and anoxia produced ischemic necrosis.

What is the relation of the hepatic changes to nonspecific ulcerative colitis which this young lady obviously had?

Most of the cases of ulcerative colitis we see here, as in other institutions, have little hepatic involvement except for nonspecific reactive hepatitis. There may be steatosis occasionally progressing to diffuse septal cirrhosis but this does not happen very often (3). Serum hepatitis sometimes progresses to post-necrotic cirrhosis (4). Bacterial cholangitis may develop, called cholangitis lenta. This was described at the Mayo Clinic (5) and since has been supported recently by a study of liver biopsy specimens (6). There may be a hyperergic

cholangitis. The only case where I have seen hyperergic cholangitis with jaundice was in one case of drug jaundice. I do not know whether there was a primary bacterial cholangitis in the present case or whether there was a hypersensitivity type of reaction. We have seen a few cases of intrahepatic bile duct carcinoma with ulcerative colitis, and that may have been from proliferating adnexal glands. This was not present in this case.

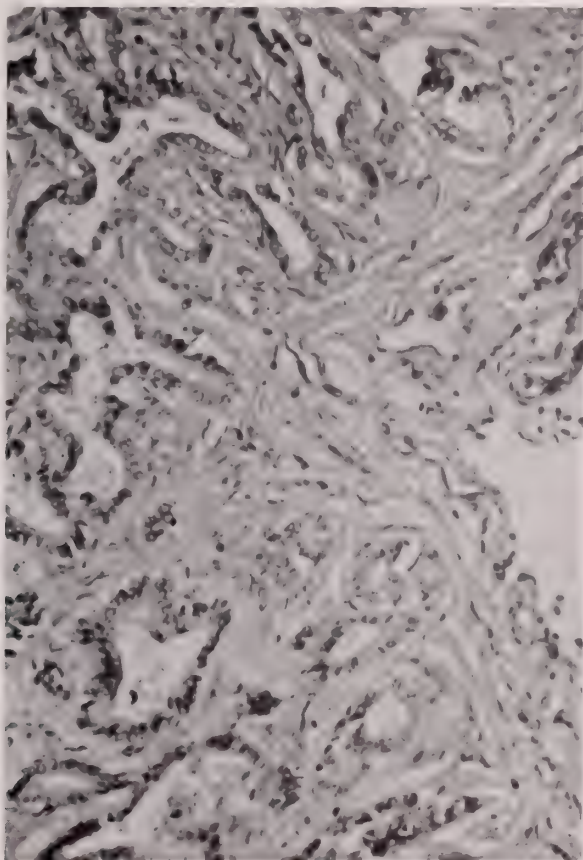


FIG. 8. Extensive bizarre proliferation of adnexal glands in wall of large bile duct. (H & E $\times 120$)

In the background were thalassemia minor, hyperchromic anemia with target cells, reticulocytosis and tendency to hepatosplenomegaly. The patient had an allergic diathesis with wheezing and drug hypersensitivity. She had a chronic nonspecific ulcerative colitis waxing and waning for 13 years.

I would explain the incident 14 years ago with 2+ cephalin flocculation, slight elevation of thymal turbidity, slight increase of alkaline phosphatase activity, prolonged prothrombin time, and BSP retention, on the basis of a serum hepatitis because after a while the prothrombin time, the BSP retention and the cephalin flocculation returned to normal. However, three years later, sclerosing

intrahepatic cholangitis began. The alkaline phosphatase activity rose very high despite low serum bilirubin levels. Intrahepatic obstruction, for instance, due to persistent cholangitis after cholecystectomy, is characterized by almost normal or only slightly elevated serum bilirubin with very high alkaline phosphatase activity. The terminal episode was hemorrhage from the colon and operation reduced from intrahepatic and extrahepatic venous shunting resulting in ischemic necrosis. Shock, cholestasis, plus whatever the thalassemia minor contributed, now produced the very severe jaundice.

In conclusion, the reason for presenting this very unusual case is to call attention to a possible complication of ulcerative colitis which is poorly known.

Final Diagnosis: 1. SCLEROSING INTRAHEPATIC CHOLANGITIS PRODUCING BILIARY CIRRHOSIS, WITH BLEEDING ESOPHAGEAL VARICES. 2. CHRONIC ULCERATIVE COLITIS (STATUS POSTCOLECTOMY). 3. THALASSEMIA MINOR.

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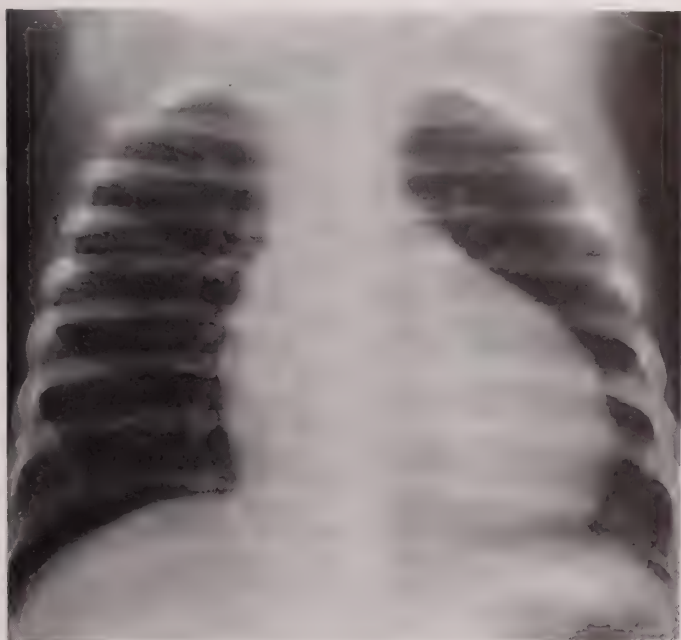
Radiological Notes

MURRAY G. BARON, M.D. AND BERNARD S. WOLF, M.D.

New York, N. Y.

CASE NO. 169

This was the first admission of a five month male infant because of cyanosis and tachypnea since birth. The cyanosis deepened during crying and feeding. Physical examination revealed the infant to be underdeveloped and cyanotic.



Case 169, Fig. 1. Examination of the chest shows the heart to be enlarged to the left with blunting and elevation of the cardiac apex. There is straightening of the upper left heart border and a normal pulmonary artery segment is not seen. There is flattening of the right atrial contour. The aortic knob cannot be identified but the aorta descends to the left of the spine. The hilar vessels are small and the peripheral pulmonary arteries have a reticular appearance.

There was no difference in the degree of cyanosis of the upper and lower extremities. The liver was enlarged although there was no significant peripheral venous engorgement. A harsh systolic murmur was heard best over the pulmonic area. An electrocardiogram showed biatrial enlargement and left ventricular hyper-

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

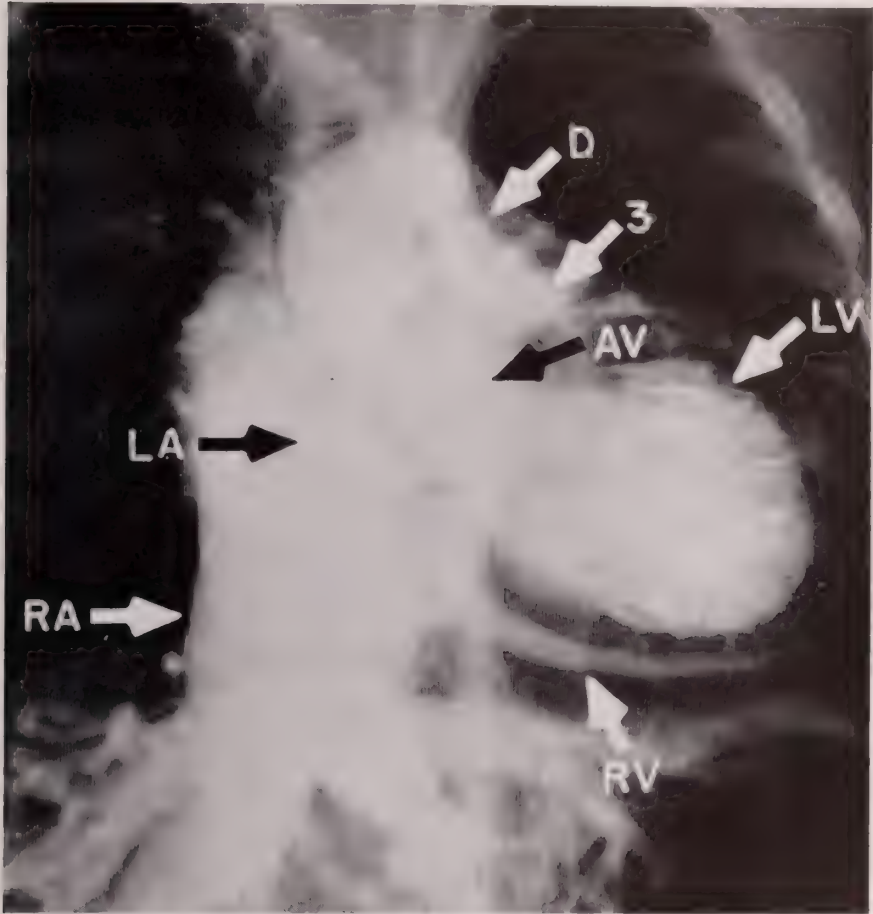
trophy. On the basis of the cyanosis and the left ventricular hypertrophy, a diagnosis of tricuspid atresia was made. A chest film (Fig. 1) showed the heart to be enlarged to the left. The apex was blunted and rounded, producing a convex



Case 169, Fig. 2A. Injection of contrast material into a right antecubital vein shows a normal superior vena cava with reflux into the left innominate vein (arrow). The right atrium (RA) is enlarged with prominent reflux into distended hepatic veins. There is early visualization of the left atrium (LA) and left ventricle (LV) indicating a right to left interatrial shunt. Note the prominent left atrial appendage (1) which forms a portion of the left heart border. There is a triangular area (2) between the right atrium and left ventricle in the area of the normal right ventricle which is not filled with contrast material.

curve to most of the left cardiac border. The interventricular notch could not be identified. There was flattening of the pulmonary artery segment. The right atrial contour was less prominent than normal. The descending aorta was located to

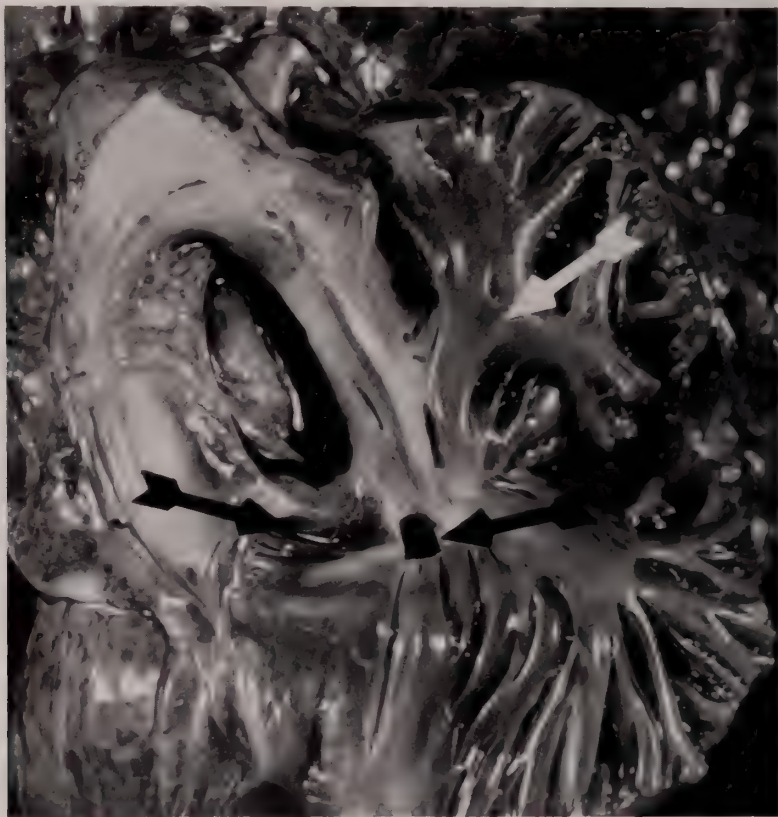
the left of the spine but the aortic knob could not be identified. The pulmonary vasculature was markedly decreased and had a reticular appearance often associated with collateral circulation arising from the bronchial arteries.



Case 169, Fig. 2B. Film taken shortly after Fig. 2A shows a slitlike right ventricle (RV) with thick muscular walls and no outflow tract. The pulmonic valve cannot be identified. The left ventricle (LV) is large and globular. Its wall is thick. The aortic valve (AV) is in its normal position. The patent ductus is in a plane perpendicular to the film and is seen as a circular area of increased density (D). Both pulmonary arteries are hypoplastic. The left pulmonary artery can be seen through the overlying left atrial appendage (3).

A venous angiocardigram showed a large right atrium and a right to left shunt at the atrial level (Fig. 2A). The septal defect itself could not be visualized because of the normal obliquity of the interatrial septum in the standard frontal and lateral projections. There was marked reflux of contrast material into large,

bulbous hepatic veins. While it is not uncommon to see some hepatic reflux from the right atrium in normals, the marked reflux in this case strongly suggested right atrial hypertension. In sequence, the next chamber to be visualized was the left ventricle, filling from the left atrium. A dilated aorta arose from the left ventricle, the aortic valve being in normal position. On late films (Fig. 2B), a



Case 169, Fig. 3A. View of the autopsy specimen looking into the right atrium from above. The foramen ovale is patent. The right atrial appendage (white arrow) is large and the trabeculae hypertrophied. The tricuspid annulus (lower right arrow) is very small and stenotic. The opening of the coronary sinus (lower left arrow) is immediately adjacent to the tricuspid orifice.

slitlike right ventricle was visualized. No sign of a right ventricular outflow tract or of a main pulmonary artery was seen. There was a patent ductus which filled small right and left pulmonary arteries. The angiocardiographic diagnosis was tricuspid atresia, pulmonary atresia and hypoplasia of the right and left pulmonary arteries.

Following the angiocardiogram, the patient's condition deteriorated rapidly and he died some time later. At autopsy (Figs. 3A, 3B), the right atrium was

found to be enlarged and hypertrophied. The foramen ovale was patent but not enlarged. A tricuspid valve was easily identified. The annulus of this valve was small, the orifice measuring about 5 mm in diameter. The tricuspid leaflets were



Case 169. Fig. 3B. View of the heart from the right side, the lateral wall folded back. The stenotic tricuspid annulus (upper black arrow) has been opened. The septal leaflet of the tricuspid valve (upper white arrow) with its short chordae tendinae (lower white arrow) is seen to arise from the wall of the right ventricle below the annulus. The whitish endocardium below the chordae is due to fibroelastosis. The right ventricular chamber is small with hypertrophic muscular wall (lower black arrow).

small and not completely separated from each other. The septal leaflet arose from the right ventricular wall below the annulus as in Ebstein's anomaly. The chordae tendinae were short. The right ventricular chamber was very small with greatly hypertrophied muscular walls. Its endocardium was thickened and white, indicating endocardial fibroelastosis. There was complete pulmonary atresia and

an intact interventricular septum. The aortic valve was bicuspid and the ascending aorta dilated. A patent ductus was present, leading to hypoplastic pulmonary arteries.

Tricuspid stenosis is a much less common anomaly than tricuspid atresia and is usually associated with other cardiac defects. These children are cyanotic because of the high grade resistance to normal right atrial emptying offered by the stenotic tricuspid valve and therefore the prominent shunting of unoxygenated blood through the foramen ovale into the left atrium. In addition, the right ventricular pressure is elevated because of the pulmonary atresia. The contour of the heart reflects the hypoplastic right and enlarged left ventricle. There is some flattening of the right atrial contour even in the presence of enlargement of this chamber because the atrium is shifted to the left into the area normally occupied by a full-sized right ventricle. The combination of tricuspid stenosis with pulmonary atresia produces essentially the same clinical and roentgenographic picture as tricuspid atresia. In both, there is a history of cyanosis from birth and left ventricular hypertrophy on the electrocardiogram. The two conditions can be differentiated by cardiac catheterization if the catheter enters the right ventricle from the atrium. However, because of the small size of the tricuspid orifice, this is unlikely. Venous angiocardiology as in this case cannot separate the two conditions because there is often an interventricular septal defect associated with tricuspid atresia and the right ventricle will be visualized by contrast material from the left ventricle. When the right ventricle is opacified by a venous injection of contrast material, the diagnosis of tricuspid stenosis and not atresia can be made if a second and selective injection is made into the left ventricle. The lack of demonstration of an interventricular shunt would then demonstrate that the right ventricle fills from the right atrium and therefore, that the tricuspid valve is not atretic.

Case Report: TRICUSPID STENOSIS AND PULMONARY ATRESIA.

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CASE NO. 170

Almost immediately after an uneventful delivery, this baby was noted to be cyanotic. The cyanosis increased when she cried. A systolic murmur in the left parasternal area was heard at this time. During the first day of life, signs of congestive failure appeared which necessitated digitalization. An electrocardiogram showed right axis deviation. Clinically, complete transposition of the great vessels was suspected. The child remained in poor condition and, on the sixth day, angiocardiology was performed to establish the diagnosis and to enable planning of a surgical approach.

A roentgenogram of the chest (Fig. 1) showed the heart to be enlarged and "egg-shaped" with a prominent right atrial contour. The superior mediastinum

was narrow and neither an aortic knob nor a main pulmonary artery could be identified. There was an increase in the pulmonary vasculature. Four cc of Ditrion was injected manually into the right saphenous vein and serial biplane films were made (Figs. 2A, 2B, 2C). The right atrium was enlarged. Contrast was seen to flow across the interatrial septum. The left atrium and right ventricle were opacified simultaneously. The aorta arose entirely from the right ventricle. The aortic valve was on the right side of the heart. On the lateral projection,

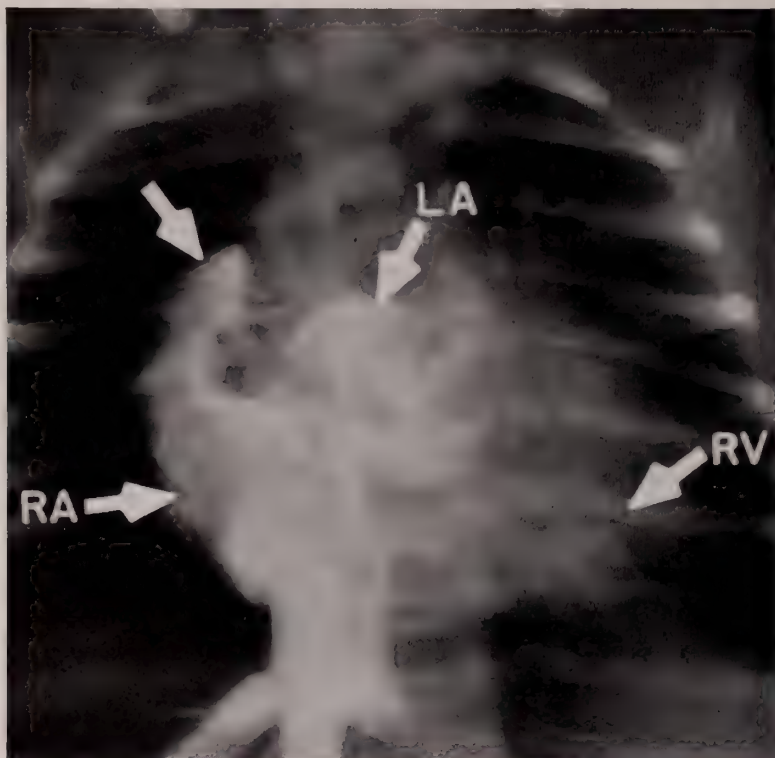


Case 170. Fig. 1. A film of the chest shows the heart to be enlarged and "egg-shaped." The right cardiac contour is very prominent and there is a localized bulge in its upper portion. This is caused by the large right atrium and its dilated appendage. The vascular pedicle is narrow. Neither the aortic knob nor pulmonary artery can be identified. The pulmonary vasculature is prominent. The gastric bubble is on the left side.

this valve was located higher and more anteriorly than normal. This produced an angular contour to the aortic arch. A small patent ductus was present but the right to left flow was not sufficient to provide good visualization of the pulmonary arteries. The roentgen features indicated complete transposition of the great vessels. The child ceased some time after the procedure.

Autopsy revealed a large right atrium with a dilated and patent foramen ovale. The left atrium was of normal size. The interventricular septum was intact and the mitral and tricuspid valves normal. The aorta arose anteriorly and to the right, from the right ventricle. The aortic valve was tricuspid. The pulmonary artery arose entirely from the left ventricle. The pulmonic valve was bicuspid. A small patent ductus was present.

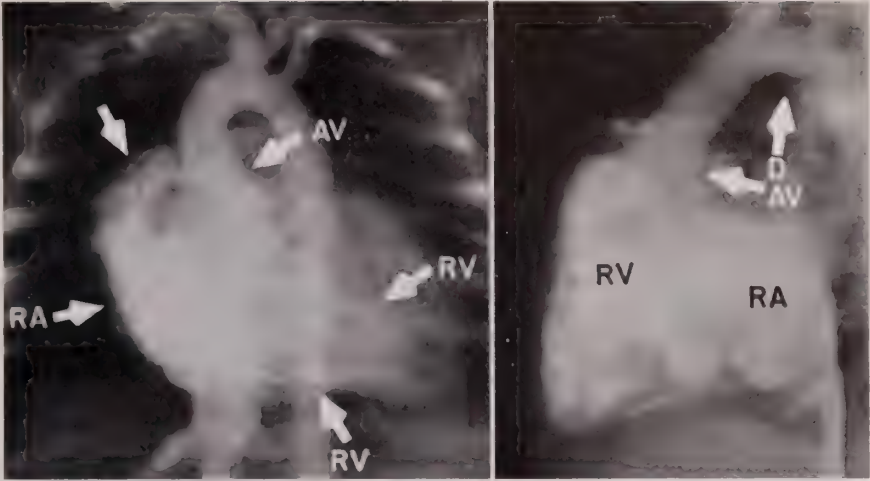
In complete transposition of the great vessels, the systemic and pulmonary circulations are separate. All venous blood from the body returns to the right side of the heart and is pumped directly into the aorta and peripheral vessels. Life is possible only if there are associated anomalies allowing sufficient blood to be shunted between the two circulations. Almost all these children die within



Case 170. Fig. 2A. An early film of a venous angiogram in the frontal plane shows slight reflux into hepatic veins. This is within normal limits. The right atrium (RA) is slightly enlarged and its appendage (unlabeled arrow) dilated and prominent. The left atrium (LA) is opacified through a right to left interatrial shunt at the same time that contrast material can be identified in the right ventricle (RV).

the first year of life but there are rare cases reported which have been followed into their teens.

The narrow vascular pedicle and "egg-shaped" heart, when present, are suggestive of some form of transposition. However, it is not uncommon for this appearance to be lacking, especially in the neonatal period. The diagnosis can frequently be made from the clinical findings but confirmation depends on angiocardiology. On the angiogram, complete transposition must be differentiated from tricuspid atresia. Both conditions are associated with large right atria, right to left interatrial shunts and often, a patent ductus. The key



Case 170. Fig. 2B. Film made 0.5 seconds after Fig. 2A shows a normally placed right ventricle (RV). The aorta arises from this ventricle, to the right of the spine. The aortic valve (AV) is situated higher than normal. The large right atrium (RA) and its appendage (arrow) are still opacified.

Case 170. Fig. 2C. In the lateral projection, the relationship of the right atrium (RA) and right ventricle (RV) is normal. The aortic valve (AV) is situated anteriorly in continuity with the right ventricle. This causes a widening of the curve of the aortic arch. The aortic end of the patent ductus (D) can be seen.

to the differentiation lies in identifying the ventricular chamber that opacifies first. In complete transposition, in the frontal plane, the right ventricle, immediately adjacent to the right atrium, fills promptly and empties into the aorta. When tricuspid atresia is present, there is a triangular area to the left of the tricuspid valve which remains nonopacified even though contrast material is seen in a ventricular chamber. This is the area of the right ventricle and will fill on later films only if there is an interventricular septal defect. Tricuspid atresia may be associated with complete transposition of the great vessels. In such instances, the diagnostic features of both conditions will be evident.

Case Report: COMPLETE TRANSPOSITION OF THE GREAT VESSELS.

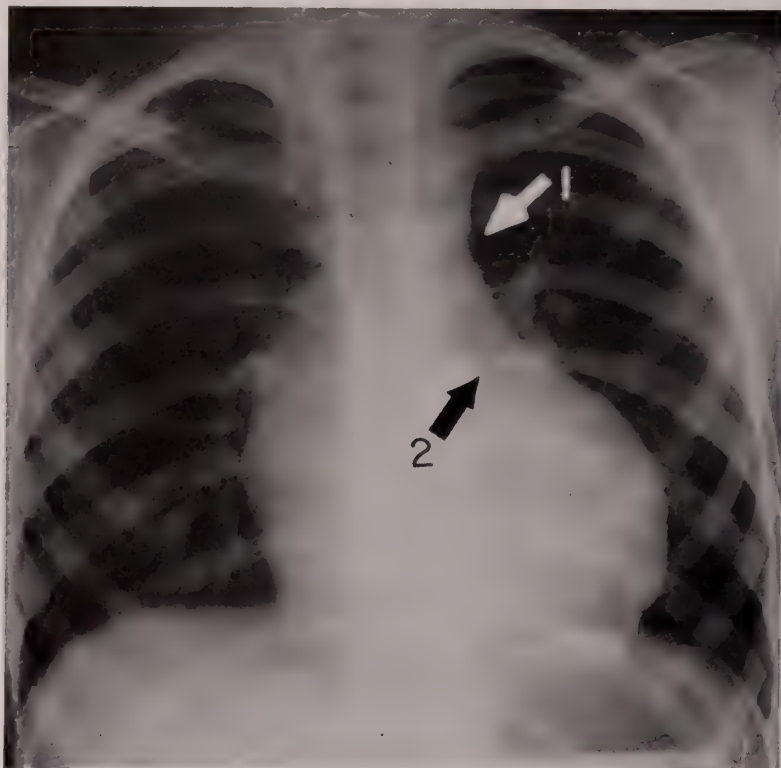
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CASE NO. 171

This six year old girl had been completely well until two years prior to admission when she began to have attacks of dyspnea and palpitations which some-

times lasted as long as a day or two. These attacks would occur suddenly, without warning, were usually associated with nausea and would end promptly following vomiting. During one such episode, she was found to have a supraventricular tachycardia with a rate of 240 per minute. When this was finally broken with digitalis, a murmur could be heard and the child was referred for



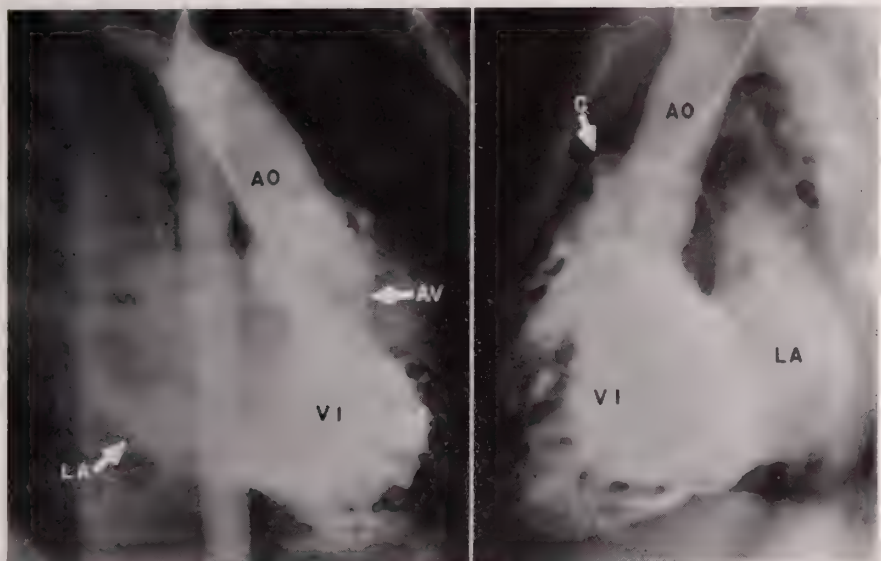
Case 171. Fig. 1. Film of the chest shows the heart to be slightly enlarged and globular in shape. There is a suggestion of an aortic knob on the left (1) but a pulmonary artery segment cannot be identified. The left main bronchus (2) is bowed upwards slightly, suggesting the presence of left atrial enlargement. The vascular pedicle is narrow. The pulmonary vasculature is normal although the right hilar vessels are less prominent than usual.

further evaluation. There was no history of cyanosis, recurrent respiratory infections or exercise intolerance.

Physical examination was entirely normal except for auscultation of the heart. A grade IV blowing systolic murmur was heard best along the left sternal border in the third and fourth intercostal spaces and a short, mid-diastolic murmur was audible just below the left nipple. The electrocardiogram revealed atypical left bundle branch block. The clinical impression was ventricular septal defect with a diastolic flow murmur. Several observers suggested the possibility of mitral in-

sufficiency. Roentgen examination of the chest (Fig. 1) showed a globular, slightly enlarged heart with rounding and elevation of the apex. There appeared to be a small aortic knob normally located on the left side. The left main bronchus was slightly elevated suggesting left atrial enlargement. The pulmonary vasculature was normal. A specific diagnosis could not be made from these films but they were considered compatible with a small ventricular septal defect.

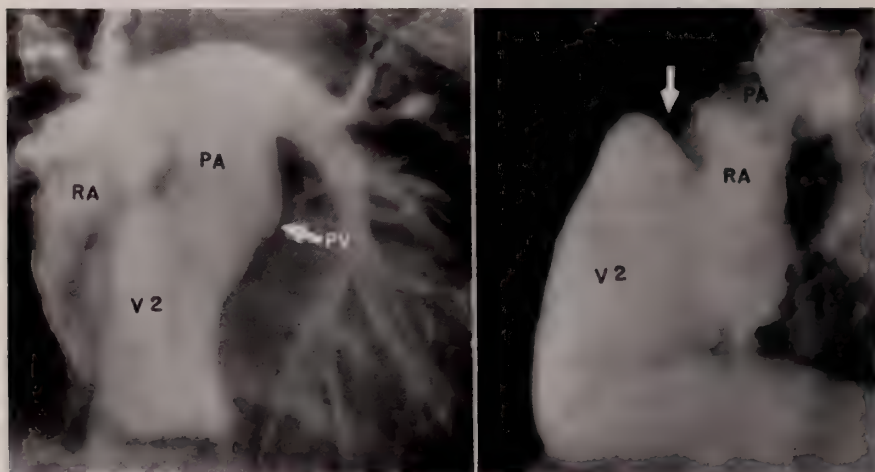
Right heart catheterization revealed normal pressures and oxygen saturations



Case 171. Fig. 2A. Frontal plane. Fig. 2B. Lateral plane. The aorta (AO) arises from a ventricular chamber situated on the left side of the heart and anteriorly (VI). The walls of this ventricle, particularly anteriorly, are thickly trabeculated. The aortic valve (AV) is in the position normally occupied by the pulmonic valve. The coronary artery (C) arising from the right aortic cusp has the distribution of a left coronary artery. A second coronary artery is not seen. There is prominent regurgitation of contrast material from the ventricle into the left atrium (LA).

in the right atrium and ventricle. Despite considerable manipulation, it was not possible to enter the pulmonary artery. Because of the possibility of a small interventricular septal defect not demonstrable by oxygen studies (see Case No. 157, Radiological Notes), it was decided to do a left ventricular angiocardiogram. A J-shaped catheter was passed via the left brachial artery through the aortic valve and Ditiokon injected with a pressure syringe (Figs. 2A, 2B). At first glance, the ventricle from which the aorta arose appeared to be the left ventricle since it was on the left side of the heart and regurgitation into the left atrium could be seen. However, this ventricular chamber was located anteriorly as seen on the lateral projection, and its walls were thickly trabeculated. The outflow tract of this ventricle was situated on the left side of the heart and anteriorly.

These features are characteristic of an anatomical right rather than left ventricle. The aortic valve was high on the left side of the heart and located anteriorly where, in the normal heart, the pulmonic valve should be seen. The ascending aorta curved gradually towards the midline and descended in its normal position, to the left of the spine. In the lateral projection, the coronary artery arising from the right or anterior aortic sinus had the distribution of a normal left coronary artery. The angiographic findings were characteristic of "corrected



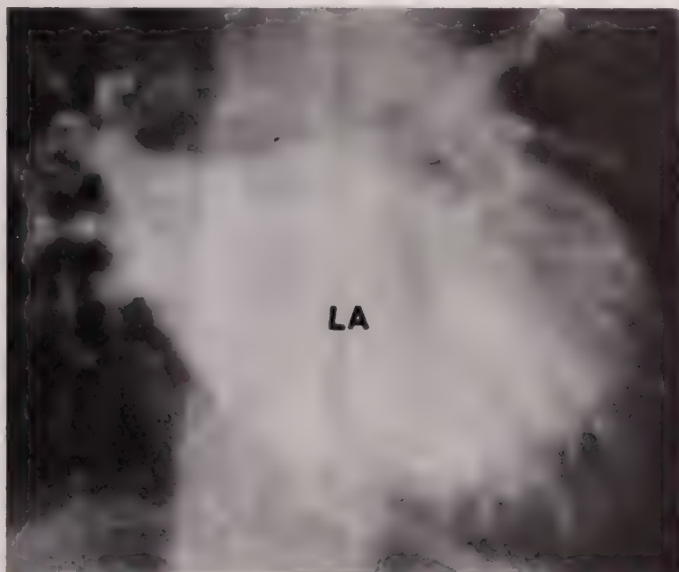
Case 171. Fig. 3A. Frontal film of a venous angiogram shows the right atrium (RA) to be normal in position and configuration. The venous ventricle (V2), filled from the right atrium, has a peculiar shape caused partly by the indentation on its left border produced by the enlarged arterial ventricle. Its walls show no trabeculation and no infundibulum is seen. The pulmonic valve (PV) is lower than normal and in the midline. The pulmonary artery (PA) is centrally located and bifurcates symmetrically.

Case 171. Fig. 3B. A lateral film made at the same time as Fig. 3A shows the venous ventricle (V2) to be located in the same frontal plane as the arterial one (Fig. 2B). The pulmonary artery (PA) arises further posteriorly than does the aorta. It is overlapped by the right atrial appendage (RA). A prominent ledge (arrow) is seen between the pulmonary artery and the anterior wall of its ventricle.

transposition of the great vessels." In addition, during ventricular systole, there was significant regurgitation of contrast material into a large but normally placed left atrium.

At a subsequent date, a venous angiogram was done to visualize the right side of the heart (Figs. 3A, 3B, 3C). Once more, the course of the blood flow appeared normal. The venous blood entered a normal appearing right atrium. This emptied into a peculiarly shaped ventricular chamber which led into the pulmonary artery. Although functioning as a right ventricle, this chamber had the anatomical characteristics of a left ventricle. Its wall was smooth, without trabeculation, and there was no evidence of an infundibulum. It was lo-

eated to the right of the arterial ventricle. The pulmonary artery was in the mid-line so that the right and left branches appeared symmetrical in the frontal plane. In the lateral view, the pulmonary artery was set back on its feeding ventricle and was not flush with the anterior ventricular wall as is seen in the normal heart. We have seen this "ledge" between the pulmonic valve and the ventricle in every case of corrected transposition and feel that it is characteristic of posterior placement of the pulmonary artery. The pulmonic valve was situated slightly behind and at a lower level than the aortic valve. A later film showed normal pulmonic veins entering the enlarged left atrium (Fig. 3C).



Case 171. Fig. 3C. A frontal film during the levocardiogram phase shows the pulmonic veins emptying into the normally located and normally shaped left atrium. The left atrium is moderately enlarged.

The term "corrected transposition" is used in a physiological sense. Despite the transposition or reversed relationship of the pulmonary artery and aorta, the sequence of blood flow is normal. Venous blood leaves the heart via the pulmonary artery and enters the lungs and arterial blood leaves via the aorta to supply the body. In "uncorrected" transposition, the aorta carries unoxygenated blood to the systemic circulation. A unique and additional feature in most cases of corrected transposition is inversion of the ventricular chambers. Venous blood flows from the right atrium into the anatomical left ventricle and out into the pulmonary artery. Oxygenated blood returns from the lungs to the left atrium, into the anatomical right ventricle, and thence into the aorta. There are in fact several different patterns of corrected transposition since the two atria, the two ventricles and the great vessels can be reversed independently of each other. The case illustrated demonstrates the most common pattern of corrected transposi-

tion. Usually, the mitral and tricuspid valves remain with the anatomically correct ventricle so that, in this case, the regurgitation from the arterial ventricle is probably through a defective tricuspid valve. Corrected transposition, in itself, is generally of no consequence to the patient. However, it is almost always associated with other congenital cardiac defects which determine the clinical picture.

Case Report: CORRECTED TRANSPOSITION OF THE GREAT VESSELS WITH INCOMPETENCY OF THE ARTERIAL AURICULO-VENTRICULAR VALVE.

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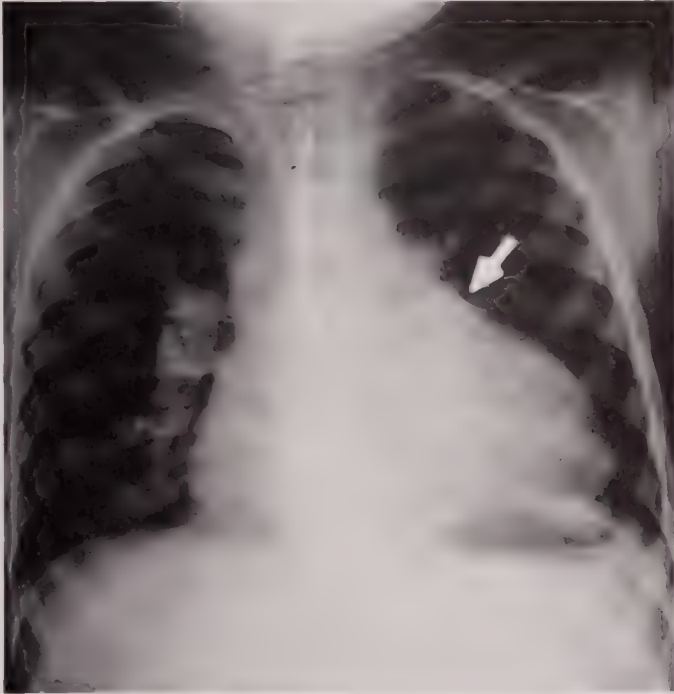
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CASE NO. 172

This boy was first seen at the age of eleven months because of retarded development and for evaluation of a heart murmur that was detected during the second month of life. There was no clear history of cyanosis or tachypnea. However, during his hospital stay, several observers described a dusky color of his fingertips and perioral region. Physical examination suggested enlargement of the heart. There was a grade IV systolic murmur heard loudest along the left sternal border and associated with a thrill palpable over the cardiac apex. The pulmonic second sound was loud and snapping in quality but not split. The electrocardiogram showed right ventricular hypertrophy. Cardiac catheterization was performed at this time. There was a significant step-up in the oxygen concentration at the level of the right atrium. The catheter could be passed across the septum into the left atrium. There was a questionable further increase in oxygenation in the right ventricle suggesting a second left to right shunt at this level. The right ventricular pressure was high, 93/13 mm Hg. The pulmonary artery could not be catheterized. During an attempt to maneuver the catheter into the pulmonary artery, the aorta was entered from the right ventricle. The peripheral arterial blood showed oxygen desaturation. The findings were interpreted as being indicative of a pentalogy of Fallot (tetralogy plus an interatrial septal defect). No corrective procedure was undertaken at this time. The child had several subsequent hospital admissions because of repeated respiratory infections but there was no limitation of his activity except on most vigorous exercise.

At the age of four years, he was readmitted to the hospital for further study. The physical findings were essentially unchanged. A film of the chest (Fig. 1) showed the heart to be enlarged in its transverse diameter. There was a localized bulge in the upper left cardiac contour in the region where the "third ventricle" is seen in some cases of infundibular stenosis. Whether the cardiac enlargement was due only to right ventricular enlargement or to enlargement of both ventricles could not be definitely determined. The pulmonary vasculature was increased as seen with a left to right shunt. The roentgen diagnosis at this time was ventricular septal defect with pulmonic stenosis. Repeat cardiac catheterization showed a 2.0 vol. per cent oxygen step-up in the right atrium and a further in-

crease of 1.4 vol. per cent in the right ventricle. Both the pulmonary artery and the aorta were entered from the right ventricle. Pressures were as follows: right ventricle—97/10, main pulmonary artery—15/6 and aorta 94/15. A pull-through tracing from pulmonary artery to right ventricle showed an intermediate pressure area in the infundibulum. These findings indicated both pulmonic valvular and infundibular stenosis, an interatrial and an interventricular septal defect. The peripheral oxygen desaturation and the oxygen step-up in the right

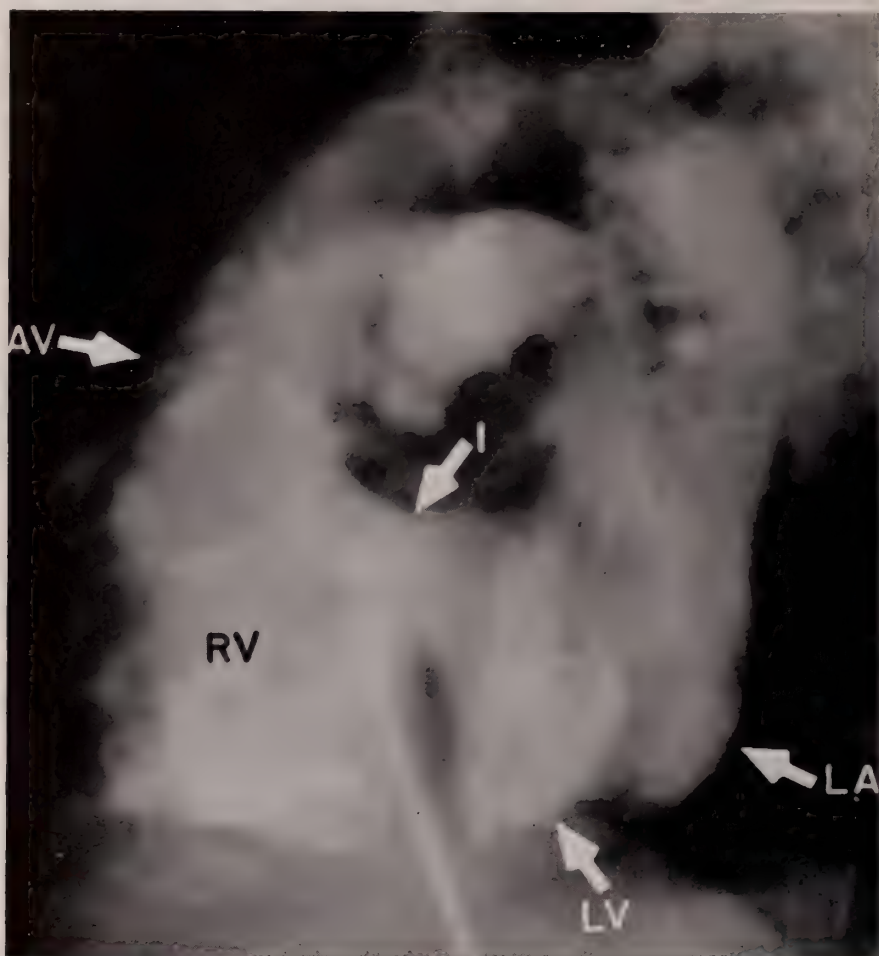


Case 172. Fig. 1. A chest film shows the heart to be enlarged, the contour suggesting right ventricular enlargement. A bulge along the upper left heart border (arrow) is caused by a dilated infundibular chamber ("third ventricle"). The aortic knob is small but in normal position. The pulmonary vessels are increased in prominence and the hilar shadows are large. This is strongly suggestive of a left to right shunt.

side of the heart indicated that the shunt was bidirectional. A selective right ventricular angiocardigram was performed but the findings appeared to be equivocal. About a year later, a retrograde, selective, left-sided angiocardigram was done via the brachial artery.

The venous (Fig. 2) and arterial (Fig. 3A, 3B) angiocardigrams showed the same features. Two ventricular cavities were seen in normal relationship to each other. However, both great vessels arose from the right ventricle. The aorta was to the right of the pulmonic artery and in the same frontal plane. Both valves were located in the same horizontal plane. The left ventricle had no outflow tract.

It received blood in a normal fashion from the left atrium and emptied through the septal defect into the right ventricle. On the late films, at the time of visualization of the left atrium, there was reopacification of the right atrium because of

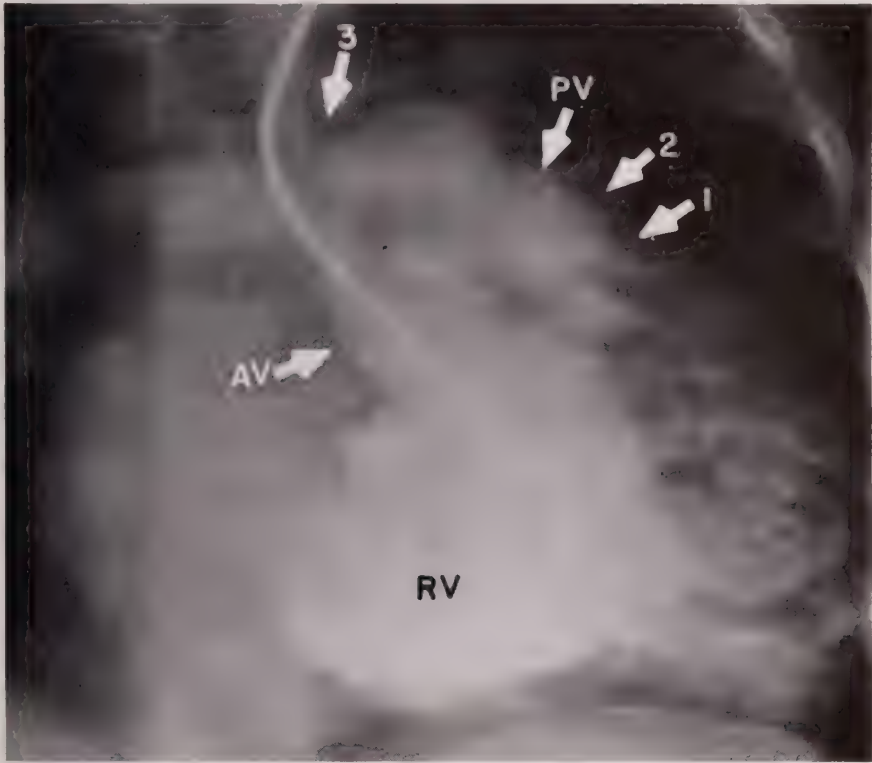


Case 172. Fig. 2. Lateral projection of a selective right ventricular angiogram. The catheter has been passed through the inferior vena cava and right atrium into the right ventricle (RV). There is a large interventricular septal defect (I). Contrast material shunted from right to left across this defect opacifies the small left ventricle (LV) which has no outflow tract. There is some regurgitation through the mitral valve into the left atrium (LA). The aortic valve (AV) is seen to be related only to the right ventricle.

the left to right shunt at this level. In the frontal plane (Fig. 3A), infundibular stenosis and the dome formed by the stenosed pulmonic valve could be identified. The roentgen findings demonstrated both great vessels arising from the right

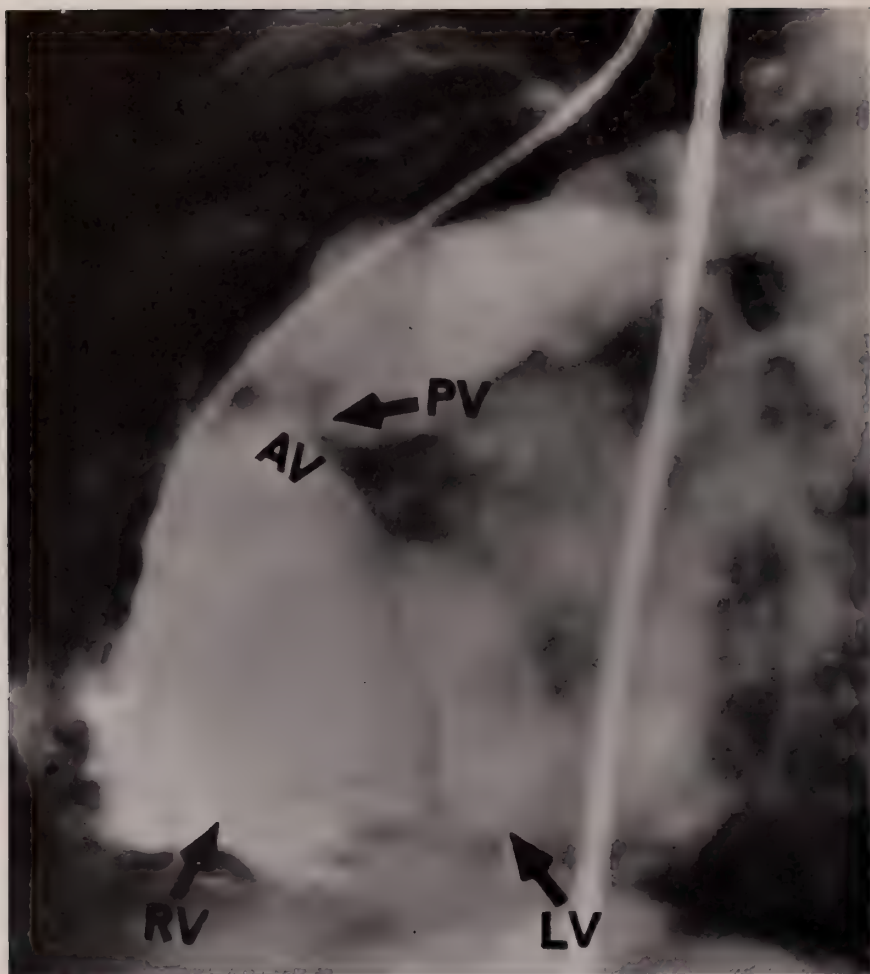
ventricle, infundibular and pulmonic valvular stenosis, interatrial and inter-ventricular septal defects.

Origin of both great vessels from the right ventricle is a rare anomaly and requires angiocardiology for a definite preoperative diagnosis. From the clini-



Case 172. Fig. 3A. Retrograde angiogram via the aorta. The catheter has been passed via the brachial artery, through the aorta, and into the right ventricle (RV). The aortic valve (AV) is to the left of its normal position and is continuous with the right ventricle. The pulmonary outflow tract is in normal position. There is a weblike infundibular stenosis (1). The pulmonic valve leaflets in systole form a dome (PV) indicating valvular stenosis. The dilated segment between the two stenotic areas (2) represents a "third ventricle." There is also coarctation of the left pulmonary artery (3) at its point of origin.

cal and therapeutic point of view, the presence or absence of pulmonic and or infundibular stenosis is of great importance. When pulmonic stenosis is present, the clinical, hemodynamic and electrocardiographic findings may be identical with those seen with a severe tetralogy of Fallot. Visualization of the blind left ventricle with both great vessels coming from the right establishes the differential diagnosis. However, in some cases, the left ventricle is never clearly outlined because there is too much dilution of the contrast material in the atria to out-



Case 172. Fig. 3B. Lateral film made at the same time as Fig. 3A. The right ventricle (RV) is large and its wall heavily trabeculated. The small left ventricle (LV) is filled via the interventricular septal defect. The undersurface of the aortic valve (AV) can be identified. The pulmonic valve (PV) partly overlaps the aortic valve and is at essentially the same level. Just before this film was made, there was an extra-systole and contrast material flowed into the pulmonary artery before the aorta. This is consistent with the smaller resistance in the pulmonary than in the systemic circulation.

line the ventricle on the levocardiogram and the right to left interventricular shunt is too small for adequate opacification. The level of the aortic and pulmonic valves is important. In the normal and in tetralogy of Fallot, the aortic valve is lower in position than the pulmonic valve. When both great vessels arise from the right ventricle, the two valves are at the same level. In addition, in tetralogy, it is usually possible to visualize the aorta astride the ventricular septum and the septal defect.

In the absence of pulmonic stenosis, the clinical picture is most easily confused with that of a large ventricular septal defect or a single ventricle. Again, differentiation depends on demonstration of the relationships of the great vessels and the presence of two ventricular chambers. When both great vessels arise from the right ventricle, the degree of peripheral oxygen desaturation may vary greatly from patient to patient. This is determined by the degree of admixture of venous and arterial blood in the right ventricle. It is not uncommon to have streamlining of the flow from the left ventricle through the septal defect and into the aorta. The oxygen saturation of the aortic blood will then be appreciably higher than that of the pulmonary artery.

Case Report: BOTH GREAT VESSELS ARISING FROM THE RIGHT VENTRICLE WITH PULMONIC STENOSIS.

ACKNOWLEDGMENT

The authors wish to express their thanks to Dr. Leonard Steinfeld, Dr. Arthur Grishman and to Dr. Alvin Gordon and the members of the Cardiac Catheterization Team for their indispensable cooperation in the study of these patients and to Dr. Lottie Strauss who was responsible for the pathological correlation and illustrations.

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Abstracts

Papers Presented Before the Research Club of The Mount Sinai Hospital

New York, N. Y.

Renal Excretion of Urate Loads in Gouty and Nongouty Man. Lawrence Berger, M.D., T'sai F. Yu, M.D., and Alexander B. Gutman, M.D.

Rapid intravenous urate loading in man yields titration curves showing marked splay and, even at the largest loads tolerated, usually equivocal saturation of reabsorptive capacity, presumably because of concurrent tubular secretion and distinct urate reabsorptive and secretory T_m 's. Berliner *et al.* (J. Clin. Invest. 1950) found an apparent reabsorptive $T_{m_{ur}}$ of ca 15 mg/min in normal man; Lathem and Rodnan (Arthr. & Rheum. 1961) report ca 10 mg/min normally and widely divergent values, 20 mg/min or more, in gout. In the present study, 7 nongouty and 7 gouty subjects, all with $C_{inulin} > 100$ ml/min except one, were infused with urate at progressively increasing rates to 20–32 mg/min (total dose usually ca 2 Gm) and maximal P_{ur} 13–16 mg%. As F_{ur} increased, in both gouty and nongouty net T_{ur} increased in parallel. The net T_{ur} curve in both groups began to flatten out at about F_{ur} 14 mg/min, maximally at F_{ur} 16–19 mg/min with net T_{ur} 11–14 mg/min. No apparent reabsorptive $T_{m_{ur}}$ could be unequivocally demonstrated for either group, despite attainment of maximal F_{ur} to 25 mg/min, net T_{ur} to 18 mg/min (13 mg/100 ml GFR) and $F_{ur}/\text{net } T_{ur}$ to 1.6. Within both groups there was considerable spread, with complete overlap. Under the conditions of the experiments, the gouty and nongouty exhibited no distinct differences in net T_{ur} or other parameter at any equivalent P_{ur} or F_{ur} level.

Pathology of Lupus Nephritis. Edith Grishman, M.D., Jacob Churg, M. D., Willy Mautner, M.D., and Y. Suzuki, M.D.

Renal changes in systemic lupus erythematosus were studied by means of 20 biopsies and at 25 autopsies. Electron microscopy was performed in ten biopsy specimens. Changes in the capillary walls and in the intercapillary spaces, focal areas of necrosis and hematoxylin bodies were observed in the glomeruli.

The capillary walls showed two apparently closely related lesions: deposits of granular material and thickening of the basement membranes. The deposits tended to localize in the basement membrane proper in the form of small electron dense patches. They were also seen under the endothelium and, in the later stages, between the basement membrane and the epithelium (podocytes). Progression of basement membrane changes led to splitting into two or more layers and eventually to actual breaks in its continuity. The capillary wall changes correspond to the well-known wire loop lesions. They differ from alterations in other diseases associated with deposits such as glomerulonephritis, nephrotic syndrome of adults (membranous glomerulonephritis), diabetes and toxemia of pregnancy, each of which shows a characteristic pattern.

The intercapillary spaces showed proliferation of mononuclear cells and of tortuous basement membrane branches accompanied by deposits similar to those

in the capillary wall. Marked expansion and eventual fibrosis of the intercapillary spaces led to capillary collapse and obsolescence of the glomeruli. The characteristic focal necrosis of glomerular loops appeared to be unrelated to the granular deposits or to the intercapillary changes.

The significance of the deposits and their relation to the basement membrane and the basement membrane branches will be discussed and the effect of steroid therapy upon the pathology of the renal disease will be evaluated.

Factors which Enhance and Inhibit Angiotensin II-I¹³¹ Degradation in Cohn Plasma Fractions. Robert L. Wolf, M.D., Milton Mendlowitz, M.D., Julia Pick, B.S., and Nosrat Naftchi, M.S. (Supported by grants from The National Heart Institute and The American Heart Association.)

Plasma from untreated primary benign hypertensive patients degrades a greater quantity of angiotensin II-I¹³¹ *in vitro* than plasma from normotensive or secondary renal hypertensive patients. The per cent angiotensin II-I¹³¹ degraded is increased by prior heat inactivation of the plasma. Twelve Cohn plasma fractions were employed in order to identify the plasma components responsible for these observations. Mixtures of angiotensin II-I¹³¹ and the Cohn fractions were refrigerated for 24 hours at 4° C and then analyzed by paper radiochromato-electrophoresis following which the strips were assayed for radioactivity. Separate angiotensin II-I¹³¹ and I-131 peaks of radioactivity were demonstrated on the radiochromatograms and the areas beneath the peaks were automatically computed by using an integrating count circuit of a linear rate-meter attached to a dual channel recorder. When the concentration of protein in the Cohn fractions was less than 1 mg/ml there was no angiotensin II-I¹³¹ degradation. The per cent angiotensin II-I¹³¹ degraded was greater than 15 per cent when the concentration of fractions I, IV-4, IV-5,6 was between 5 and 10 mg/ml. The per cent angiotensin II-I¹³¹ degraded by fraction V was increased tenfold by prior incubation at 57° C for 30 minutes. The presence of a heat labile inhibitor of angiotensin II-I¹³¹ degradation with the electrophoretic and cold-ethanol characteristics of albumin is suggested by these results.

Electrophysiology of the Brain Stem Oculomotor System. Howard P. Krieger, M.D. (Aided by Grant B1040, N.I.N.B.D., U.S.P.H.S.)

The brain stem oculomotor system in alert, cervically transected cats was investigated with electrophysiologic technics. The vestibular nuclei or the brain stem oculomotor system lying between the vestibular and third nerve nuclei were stimulated electrically. The evoked response in the third nerve rootlets and concomitant evoked eye movements were studied.

The vestibular-third nerve pathways were found limited to the paramedian zone but did not constitute a histologically discrete structure. These pathways included but were not limited to the median longitudinal fasciculus. Both slow and fast conduction systems were found in these pathways. These two systems were differentially affected by anoxia, anesthesia and repetitive stimulation. Paired vestibular stimuli enabled measurement of the duration of the effect of a single vestibular stimulus. Alteration of frequency of stimulation adduced evi-

dence that to effect eye movement summation is required at the third nerve nucleus.

These findings may help in part to define the physiology of the clinical effects of anesthesia, brain stem disease and depressed states of consciousness on eye movements.

Histochemical Correlation of Glucose-6-Phosphatase Activity with Development of Hepatocellular Carcinomas in Rats fed 3¹Me-DAB. Stanley Goldfarb, M.D., and Frederick G. Zak, M.D.

Rats fed 3¹Me-DAB show gradual loss of hepatic glucose-6-phosphatase (G-6-Pase) activity and subsequently many hepatocellular carcinomas. The reversibility of the G-6-Pase loss was studied in animals fed 3¹Me-DAB for different time intervals and returned to normal diet. Because of the heterogeneity of the liver tissue, a histochemical rather than chemical approach was employed. One group was fed the drug for 26 days, a total dosage known to induce carcinomas in low incidence, and then fed a normal diet. At the time of discontinuation, livers showed severe injury, loss of hepatocellular basophilia and rather diffuse decrease in G-6-Pase activity. After four months on normal diet the injured parenchyma was almost completely replaced by normal liver and G-6-Pase activity was practically normal. A second group was fed the drug for 39 days in a dosage known to induce carcinomas in high incidence. Striking hepatic nodular alterations, many of them regenerative in type, was associated with focal return of G-6-Pase activity. Animals returned to normal diet showed persistent large foci of swollen cells with decreased G-6-Pase activity and overall lessening of regenerative activity. Carcinomas deficient in G-6-Pase were present in high incidence three months after discontinuation. Therefore, persistent nodules of G-6-Pase deficient cells appear to be associated with induction of hepatocellular carcinoma.

The Occurrence of Extracellular Enzyme-Carrying Granules in Organs of the Reticuloendothelial System. Hans H. Baruch, M.D.

Cells of the reticuloendothelial system are characterized by the presence of high acid-phosphatase activity which can be demonstrated by histochemical staining. This activity is localized within cytoplasmic granules (phagosomes) which may be identical with the lysosomes of de Duve. Administered foreign substances engulfed by phagocytic cells are found within these enzyme-containing organelles. It was noted that in addition to the intracellular acid-phosphatase containing granules, there are present in the lymph-nodes, spleen and thymus of the rat under various experimental conditions such as administration of typhoid vaccine, Cytoxan and various colloids, similar extracellular granules. These are also present to a lesser extent in apparently normal animals.

These granules are interpreted as representing phagosomes of phagocytic cells which have been released, probably due to the death of the cell but possibly also by extrusion from living cells. Their presence in normal animals suggests that this may be a physiological response which is intensified in the presence of various agents affecting the reticuloendothelial system. It is suggested that the pres-

ence extracellularly of enzyme-containing particles may provide a mechanism by which the enzymatic decomposition of foreign substances may continue for a period of time even after the death of the phagocytic cell.

Vasolastine in the Treatment of Angina Pectoris: A Preliminary Report. Harry L. Jaffe, M.D., and Emanuel Stein, M.D.

Vasolastine contains three enzymes: lipase-citrogenase, amino-oxydase and tyrosinase-tryptase, and has been used in Europe in treating arteriosclerosis, particularly coronary and cerebral. Animal experiments suggest that Vasolastine prevents or cures artificially induced atherosclerosis. It is believed to remove lipoids and calcium deposits from the walls of arteries, and it has been shown to restore their elasticity to a varying degree.

During the past year 27 patients with chronic angina have been treated with Vasolastine for not less than six months in order to diminish the effect of spontaneous remissions, the psychological factor and of seasonal changes. All had failed to respond to the usual medical therapy and some also to one or more special procedures (radioiodine, radiotherapy, internal mammary ligation). A detailed history of the angina and effort capacity was kept before and after treatment.

Two cc of Vasolastine were injected intramuscularly twice weekly. If improvement occurred after several months, the interval was lengthened. Not a single local or general reaction has been noted. The anticipated difficulty in evaluating therapy in angina was encountered. Approximately two-thirds were considered to show significant improvement, *i.e.*, they were able to walk at least eight or ten blocks, as against one to three, and required 75 per cent fewer nitroglycerin tablets. A significant number of patients continued to improve after stopping the injections; others had to resume them. Treatment of a large series is essential to confirm these initial encouraging results, this will be done in a double blind study.

Important Notice

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THE JOURNAL OF
THE MOUNT SINAI HOSPITAL

In Memoriam

WILFRED C. HULSE

1900-1962

Dr. Wilfred C. Hulse died suddenly following a coronary occlusion on January 9, 1962, after a concert. The circumstances of his death typify an active cultural, professional and charitable life lived fully and productively.

He was born in Germany in 1900, the son of a doctor; his wife and two brothers are also physicians. As is the European custom, he selected his medical training at three universities: The University of Wurzburg, University of Munich and the University of Breslau, receiving his M.D. degree in 1924. Like other German fraternity students, he bore scars of fencing duels. He met his wife at the University and married in 1929. He practiced in Berlin as a pediatrician and child psychiatrist from 1928 to 1933. A great honor there to so young a Jewish physician was his election to the executive committee of the equivalent of our county medical society. He also served as editor of two medical journals.

He left Germany in 1933. Previously, despite a warning, he courageously issued a political statement which led to a short imprisonment. He went to Paris and finally to Tunisia where he practiced until receiving a United States visa in 1935.

Settling in New York, he immediately became very active in medical and community affairs. He worked diligently for his less fortunate refugee compatriots. He started a philanthropic organization for German refugees, the Blue Card, and continued as its president until his death. He initiated the German-Jewish club which later became known as The New World Club. He founded and was president of an Immigrants' Conference. He edited a German publication "The Aufbau, an American weekly," which changed under his direction from a small monthly paper to a weekly with a circulation of 25,000.

One may wonder how he could do so much community work since he served as a consultant psychiatrist for the Salvation Army, the Lenox Hill Hospital, The Mount Sinai Hospital and later the Northport Veterans Administration Hospital, the Hillside Hospital, the Community Service Society of Long Island, the Sheltering Arms Children's Service, the Guild of the Jewish Blind and the Foster Care Division of the Department of Welfare. For a period he was Clinical Associate Professor of Psychiatry of New York State University and in January 1962 assumed a similar appointment at the Albert Einstein Medical School. He was a recognized outstanding leader and contributor to group psychotherapy and served as President of the Eastern Group Psychotherapy Association from 1959 to 1961, and currently a nominee for President of the American Group Psychotherapy Association. In 1961 he became President of the New York Council of Child Psychiatry. He published over seventy professional papers. He was a Diplomate of the American Board of Pediatrics and



WILFRED C. HULSE, M.D.

1900-1962

the American Board of Neurology and Psychiatry in Child Psychiatry, and a fellow, in addition to other memberships, of the American Psychiatric Association, the American Orthopsychiatric Association, the American Academy of Child Psychiatry, and the New York Academy of Medicine.

We had our most close association in the development of the Child Psychiatry Division of The Mount Sinai Hospital. He came to the hospital originally in 1936, working in child psychiatry with Dr. Ira Wile of the Department of Pediatrics. He interrupted this work to enlist in the United States Army early in World War II, and served as a Major overseas in England, Normandy, Belgium and Paris. Afterwards, he advanced at our hospital from Senior Clinical Assistant Psychiatrist to Adjunct Attending Psychiatrist and Associate Attending Psychiatrist. Though a few years ago he went "off service" due to the age ruling, he continued by request as an active teacher in our training program.

These accomplishments give only a small perspective of the scope of the man. A linguist, a voracious reader, interested in music, art and theatre; and always a sincere helpful friend and a considerate humane person, he helped innumerable people. Even many of his closest associates knew very little about these efforts conducted with unusual modesty and humility.

He is survived by his wife, Ilsa, a daughter Irene, and two grandchildren.

ABRAM BLAU, M.D.

for the

Editorial Board



LEONARD ELIHU FIELD

1910-1962

In Memoriam

LEONARD ELIHU FIELD

1910-1962

Leonard Elihu Field died on February 6, 1962. On this day the hospital lost a most devoted worker; his patients, a dedicated and sincere physician; while his many friends and colleagues have been deprived of the association of a truly warm human being.

Dr. Field was born in Brooklyn, New York City on August 14, 1910; he attended the University of Pennsylvania, where in 1936 he received his doctorate in medicine. He interned at The Beth Israel Hospital, New York City from 1936-1937, and successively served as Fellow in Pathology, at The Mount Sinai Hospital, New York City, from 1937-1939 and as resident in medicine at the Montefiore Hospital, New York City 1939-1940. He then returned to The Mount Sinai Hospital, New York City where he was research assistant in cardiology, and Senior Clinical Physician of the Cardiac Clinic. In addition, he participated as a faculty member of Columbia University for post-graduate teaching since 1947. He was a lucid and splendid lecturer. During the war, Major Leonard Field had been assigned, in the main, to the South Pacific from 1941-1946 where he served as electrocardiographer, chief laboratory officer, and cardiologist of his Station Hospital. On March 21, 1950 his marriage to Beatrice Epstein brought the joyful companionship he so much deserved.

In 1953 Leonard Field was invited to join the attending staff of The Hospital for Joint Diseases, in New York City, where in 1956 he was advanced to the status of Associate Physician, which he held concurrently with the position of cardiologist to the hospital to the time of his death. He was a member of The New York Academy of Medicine, the American Federation of Clinical Research, The New York Pathological Society, the American College of Cardiology, The American Society of Clinical Pathologists, the American Heart Association, the American College of Physicians, in addition to the American Medical Association and its county subsidiaries.

Despite the time devoted to a busy practice and clinical and teaching hospital responsibilities, Leonard Field was actively engaged in investigative cardiology, and indeed, made a number of significant contributions to the medical literature, some of which have already been alluded to as classics in the field of cardiology. Untiring Dr. Field, moreover, found the time, the interest and energy to conscientiously participate in his synagogue and world zionist programmes. Here, as well, he proved himself to have been a potent force and an esteemed and effectual worker. Finally, with so many admirable attributes, his greatest qualities were his deep warmth, gentleness, and compassionate tolerant understanding. It was an honored privilege to have been numbered amongst his many friends.

HENRY HORN, M.D.
for the
Editorial Board

PATTERNS OF BONE CHANGE IN THE RETICULOENDOTHELIOSIS

JOHN E. MOSELEY, M.D.

New York, N. Y.

HISTIOCYTOSIS X

(EOSINOPHILIC GRANULOMA, LETTERER-SIWE DISEASE
AND SCHÜLLER-CHRISTIAN DISEASE)

For some time now evidence has been accumulating from many quarters which appears to support the concept that eosinophilic granuloma, Letterer-Siwe disease and Schüller-Christian disease are interrelated manifestations of the same basic pathologic process (1-6). Lichtenstein (7), reviewing his own pathological material and that of others, has concluded that the pathologic common denominator of all three syndromes is an inflammatory histiocytosis which, at least for the present, has been designated histiocytosis X. This concept, however, cannot be considered proved as yet and there are those, like Otani (8), who hold strong opinions to the contrary. Nevertheless, there is a variety of conditions included in this disease complex which cannot be satisfactorily classified if one adheres too rigidly to the traditional terminology embracing three distinct diseases. Not infrequently it is impossible for a pathologist, viewing a single biopsy specimen, to state confidently in which category a particular patient belongs and multiple biopsies taken from different areas of the same patient may show characteristics consistent with all three conditions. Furthermore, one cannot be certain when confronted with a single lesion whether the disease will remain localized or will subsequently become disseminated.

Until the etiology or etiologies of these conditions are discovered and their true pathogenesis is accurately described it may be less confusing to consider them within the framework of Lichtenstein's classification. He has suggested that histiocytosis X be divided into three phases of a single disease process: 1) histiocytosis X localized to bone. The lesion may be solitary or multiple (eosinophilic granuloma); 2) acute or subacute disseminated histiocytosis X (Letterer-Siwe disease) and 3) chronic disseminated histiocytosis X (Schüller-Christian disease). It should be fully appreciated, however, that in some instances a localized condition may become disseminated, an acute case may become chronic and a chronic case may show acute exacerbation. Nevertheless, despite the fact that some cases tend to be transitional, the clinical features of each of the three syndromes generally remain distinct enough to warrant individual descriptions.

Clinical Syndromes

Histiocytosis X localized to bone (eosinophilic granuloma). Eosinophilic granuloma was first described by Otani and Ehrlich (9) and by Lichtenstein

From the Department of Radiology, The Mount Sinai Hospital, New York 29, N. Y.

and Jaffe (10) as a solitary bone lesion. Since their descriptions lesions of similar histological appearance have been found as multiple defects in the skeleton and have been demonstrated in extraskkeletal locations. When these lesions remain localized to the skeleton without constitutional evidence of generalized disease they represent the mildest form of histiocytosis X and have an excellent prognosis. This condition occurs predominantly in infants, children and young adults although it may be seen occasionally in older adults. Avery *et al.* (11) have reported a solitary eosinophilic granuloma of the frontal bone in a patient sixty-one years of age. Although practically any bone may be involved, there is a predilection for the bones of the skull, pelvis and extremities. There may be some mild fever but when symptoms are present they are referable to the local lesion and consist of local pain, swelling and occasionally heat. The histologic picture is characterized by large numbers of eosinophils, histiocytes which may or may not show lipidization and areas of focal necrosis.

Acute or subacute disseminated histiocytosis X (Letterer-Siwe disease). Disseminated disease marked by a rapidly progressive course is most often seen before the age of two years. It may be encountered, however, in young adults. The clinical picture of this syndrome may also appear terminally in chronic disseminated histiocytosis. There is evidence of a debilitating disease with fever, generalized lymphadenopathy, hepatosplenomegaly and frequently otitis media. A hemorrhagic tendency gives rise to petechiae and purpura. There is a progressive anemia. The skeleton may or may not show radiographic evidence of bone destruction. When bone lesions are present they are similar in appearance to those seen in eosinophilic granuloma and Schüller-Christian disease although Saenger and Johansmann (12) have described widening of the medullary cavities and thinning of the cortices in one of their cases. There are characteristic cutaneous manifestations which consist of discrete yellowish-brown maculopapular lesions or papules with a red border and yellow center. These occur most often over the face and trunk but may be found elsewhere. Whitish macules may develop on the palate and tongue. Weeping erosions and tender swellings sometimes develop in the axillary, genital and perianal regions. It is common for cutaneous lesions to be the first manifestation of the disease. Review of the literature on this syndrome will reveal numerous cases in which infants presented with cutaneous lesions the nature of which was not appreciated until some weeks or months later when other evidences of the disease became apparent. Tiny nodular densities due to histiocytic infiltration may appear diffusely scattered throughout the lungs. These may simulate disseminated hematogenous tuberculosis. Secondary infection is common and a bronchopneumonia may become superimposed. If survival is prolonged the interstitial granulomatous lesions may be associated with pulmonary emphysema. Such an appearance can be difficult or impossible to differentiate from fibrocystic disease of the pancreas. In an occasional case, lung lesions may be the predominant finding early in the course of the disease. This syndrome should certainly be included in the differential diagnosis of diffuse interstitial pulmonary lesions in infants, the list of which has grown considerably in the

past few years. As a rule the condition runs a rapidly fatal course in a few months or possibly a year or two; but it is not always fatal and may occasionally become chronic or develop a remission. Cases have been reported which terminated in a monocytic leukemia (13) and we have also seen one which came to such an end. Histologically the predominant picture is that of a proliferation of nonlipidized histiocytes but eosinophils and lipid containing histiocytes may be present in varying proportions.

Chronic disseminated histiocytosis X (Schüller-Christian disease). This syndrome of chronic disseminated disease begins perhaps most commonly within the first five years of life but may be encountered at all ages up to middle adult life. Its course may include spontaneous remission or periods of improvement and the ultimate prognosis is relatively good compared to that of the Letterer-Siwe syndrome. In a recent review of 29 cases (11) the mortality was 13 per cent. Earlier descriptions of this syndrome considered the classic triad of skull defects, diabetes insipidus and exophthalmos to be typical. Analyses of most series of recent cases, however, indicate that the concurrent existence of all three elements of the triad is the exception rather than the rule (11, 14). Actually one or two of these signs are apt to be found in conjunction with several other manifestations. Chronic otitis media is a common finding and, in fact, is the most frequent presenting complaint. Skin lesions and mucous membrane ulcerations may appear and resemble those seen in Letterer-Siwe syndrome. Loose teeth have been a common finding and are not infrequently one of the initial complaints. Hepatosplenomegaly and lymphadenopathy, although at times outstanding, are not as common as is generally considered. Anemia is relatively infrequent and Avery *et al.* (11) found it to be rare in their 29 cases. There may be pleural and pulmonary involvement which may remain asymptomatic and resolve after varying periods of time but in some instances the diffuse bilateral interstitial infiltrations may result in fibrosis, honeycombing of the lungs and eventual cor pulmonale and right heart failure. Spontaneous pneumothorax has been reported in a number of cases. The histologic findings include lipidized and nonlipidized histiocytes, eosinophils and fibrosis. Lipidized histiocytes tend to predominate. Attention has been called above, however, to the perplexing histologic variations that may occur in these syndromes.

Bone Lesions in Histiocytosis X

The Letterer-Siwe syndrome typically runs a rapid course and may eventuate in early death without the development of radiographically demonstrable bone lesions. A certain percentage of these cases, however, do show roentgen evidence of skeletal involvement at some time during the course of the disease but *the incidence of bone lesions is decidedly less in the Letterer-Siwe syndrome than in the Schüller-Christian syndrome.* In the latter syndrome extraskeletal manifestations without demonstrable bone lesions may be evident for varying lengths of time but continued follow-up of these patients will show eventual bone involvement in the vast majority of them. More commonly, however, bone lesions are demonstrable fairly early. Nevertheless, it should be understood that

since the early descriptions of these syndromes we have come to learn that *the demonstration of bone defects is not necessary for the diagnosis* of either one of them. Eosinophilic granuloma, on the other hand, by the presently accepted definition, always shows single or multiple lesions localized to the skeleton.

In acute and chronic disseminated disease the finding of bone lesions may be of paramount importance in arriving at an early diagnosis. Although the classic triad of skull defects, diabetes insipidus and exophthalmos is a widely known feature of Schüller-Christian syndrome, the less familiar but frequently present manifestations of the two syndromes are all too often the presenting complaints and offer many diagnostic possibilities. In such instances one is not likely to obtain any real help from blood studies or other laboratory aids short of biopsy and the roentgen skeletal findings may provide the first clue to the diagnosis.

The bone lesions which occur in the various forms of histiocytosis X are radiographically indistinguishable and are due to destruction of bone by granulomatous tissue composed principally of reticuloendothelial cells and their derivative cells, the histiocytes. It should be noted that Saenger and Johansmann (12) have observed widening of the medullary cavity and thinning of the cortex in one of their five reported cases of Letterer-Siwe disease. Although osteoporosis may develop as these children become more debilitated, widened medullary cavities and unusual cortical thinness have not been a feature of any case we have observed. *In practically all studies the bones of the skull are those most commonly affected.* The pelvis, femurs and ribs are also common sites of involvement but any bone may be involved. It is often stated that the bones of the hands and feet and the epiphyses are not affected but lesions in the tarsal and carpal bones, the metatarsals and metacarpals and phalanges may be seen occasionally and epiphyseal lesions, though rare, may also occur. While the bone lesions are primarily destructive and result in areas of increased lucency the characteristics of any particular lesion will depend on its stage of evolution when seen and whether or not it has been previously subjected to radiation or other therapy. Early lesions may consist of round or oval areas of rarefaction of various sizes in the medullary portion of the bone. (Fig. 1). These most often have well defined margins but no peripheral bone condensation. Such a lesion may be single or the lesional area may be involved by multiple circumscribed zones of radiolucency which are grouped together and in some cases appear to overlap each other (Fig. 2). An interesting feature of some lesions is *beveling of the edges which appears to add the dimension of depth.* This three-dimensional appearance has been a significant diagnostic factor in our experience. On occasion two areas differing in degree of rarefaction overlap with the appearance of a "hole within a hole" (Fig. 3). This feature also has substantial diagnostic value. Less often the lesions may be poorly circumscribed, the periphery merging with normal bone. In some cases, notably in the long bones, bone destruction may be uneven and the resulting appearance is one of coarse reticulation of the involved area by strands of surviving bone.

As the granulomas expand there is pressure atrophy of the adjacent cortex

which becomes scalloped along its inner margin. The cortex eventually may be destroyed or pathological fractures may develop at the site of the lesion. In the long bones, particularly when the cortex is destroyed by the disease process, there may be periosteal new bone formation which occurs in single or mul-



FIG. 1. *Letterer-Siwe Syndrome*. There are multiple well-circumscribed areas of bone destruction in both femora. A large lesion in the left femur is eroding the inner margin of the cortex. The patient was a 20 month old male who was normal during his first year except for persistent seborrhea involving the scalp and eyebrows. During the early part of his second year skin erosions developed in the perianal and genital regions. A few months later papular eruptions appeared on his face and trunk and several lumps were palpated on his head. On admission to the hospital he was found to have an elevated temperature, hepatosplenomegaly and anemia. Skin and lymph node biopsy revealed proliferating histiocytes and occasional foam cells.

multiple layers. The appearance may simulate Ewings's sarcoma or osteomyelitis (Fig. 4, 5). Periosteal reaction is not seen with skull lesions nor is it always seen in areas of cortical destruction in long bones. Although expansion of affected

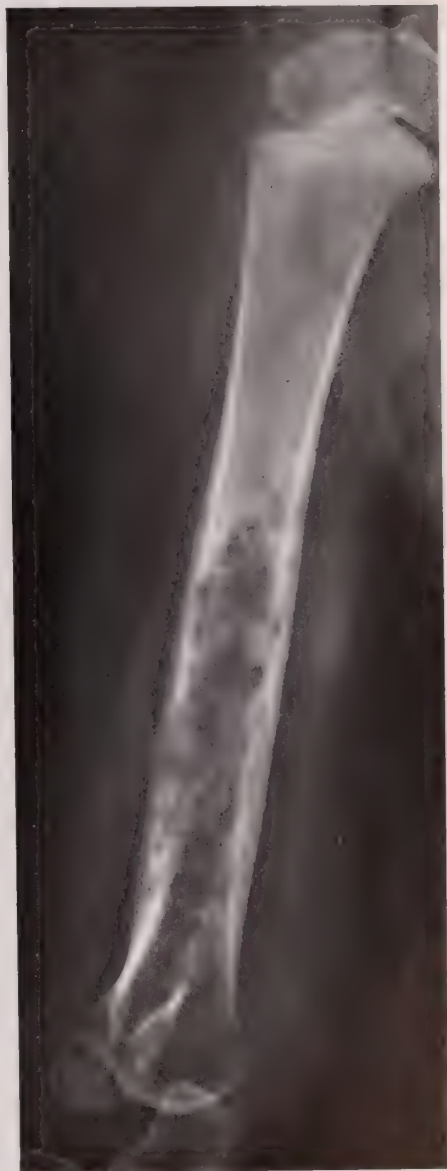


FIG. 2. *Schüller-Christian Syndrome*. There is an extensive area of involvement in the shaft of the right humerus. Overlapping and confluent areas of destruction have scalloped the inner aspect of the cortex and perforated it in some places with resultant "layer" type periosteal reaction. The patient was a four year old female with multiple bone involvement, unilateral exophthalmos, loose teeth, papular and petechial skin lesions, and slight hepatomegaly. The spleen was not palpable and there was no anemia.

ribs is commonly seen, expansion of the shaft of a long bone is uncommon. What appears to be expansion in most instances is widening of the bone contour by periosteal layering and not true dilatation.

With spontaneous healing, or after therapy, the destructive area tends to



FIG. 3. *Schüller-Christian Syndrome*. There are multiple well-circumscribed areas of destruction at the distal end of the humerus. In one area there are overlapping shadows differing in degrees of rarefaction and producing a "hole within a hole" appearance.



FIG. 4. *Eosinophilic Granuloma*. There is a large sharply margined area of destruction in the medullary cavity of the right femur. The adjacent cortex is eroded and there is a multiple layer or onion skin type of periosteal reaction. There were no other bone lesions. The patient was a five year old male whose complaint was pain in the right thigh and localized tenderness. Biopsy report was eosinophilic granuloma. The lesion was curetted. No new lesions have appeared during four years of observation.

develop a sclerotic periphery. If healing progresses the degree of rarefaction diminishes, the area loses its margination and gradually blends with the surrounding bone until finally it no longer can be seen. During this process when



FIG. 5. *Schüller-Christian Syndrome*. There is an area of destruction in the midshaft of the right humerus. There has been slight dilatation of the bone in the involved area. The regional cortex is thinned and eroded in some places with resultant layer type periosteal reaction. The patient had multiple bone involvement, exophthalmos, loose teeth, draining ears, mild hepatomegaly and interstitial pulmonary infiltrations.

rarefaction is only slight the lesion sometimes can be appreciated only by the regional cortical scalloping (Fig. 6).

In some cases, on the other hand, healing, particularly after roentgen therapy, may be characterized by osteosclerosis. The trabeculae in the involved area increase in number and thickness and there may be new bone laid down along



FIG. 6. *Schüller-Christian Syndrome*. There is a healing lesion at the distal end of the tibia. Although the medullary defect is filling in with new bone trabeculae the regional cortex is still scalloped and there is a hazy curvilinear inferior border of increased density.

the inner aspect of the cortex. Eventually the lesion is replaced by sclerotic bone which in time may itself resolve leaving a completely normal appearance. Demonstrable bone lesions may appear and progress with surprising rapidity. On serial examinations large lesions may be seen to disappear completely within



FIG. 7. *Schüller-Christian Syndrome*. There are poorly margined lesions in both tibiae. The large defect in the left tibia has a beveled edge which creates the impression of depth. In some areas of both bones the cortex is scalloped and perforated and there is periosteal reaction. There is a cortical lesion in the right fibula.

two or three months. During the same interval, new well-developed lesions may appear in the same bone. Many lesions persist for long periods, however, or show only very slow resolution (Figs. 7-9).

Although most of these granulomas arise in the medullary cavities *occasionally some of them appear to originate in the cortex* (Fig. 7). Cortical lesions may also perforate and give rise to periosteal reaction.

The Flat Bones

The skull, pelvis, ribs and scapulae are common sites of involvement and lesions in these bones have some characteristics which warrant special mention.



FIG. 8. *Schüller-Christian Syndrome*. This is the same patient shown in Fig. 7 one year and seven months later. The areas of destruction have been replaced by new bone. During the interval between examinations the patient had been on corticosteroid therapy. The generalized demineralization of the bones resulted from administration of the steroids.

The skull is the most frequently involved part of the skeleton in all three syndromes. Other parts of the skeleton may be involved, however, in the absence of skull lesions. While any portion of the skull may be affected, the calvarium is the site most often involved. The lucent lesions may vary considerably in size and shape and can range from tiny lucent defects to large irregular and conglomerate areas which have a map-like appearance. In this latter instance

the appearance is referred to as the "geographic" skull and is highly diagnostic of acute or chronic disseminated histiocytosis X (Fig. 10-12). As these lesions heal, spontaneously or after therapy, they lose their well-defined borders. Wells



FIG. 9. *Schiller-Christian Syndrome*. There are old healing lesions together with newer destructive lesions in the shafts of both femora. The patient had been given roentgen therapy to these sites and was on steroid therapy at the time of this examination.

(15) has described an area of opacity within these rarefactions in lesions diagnosed as eosinophilic granuloma, the "button sequestrum" of Wells, but such an appearance must be uncommon. The lesions rapidly extend beyond the con-

fines of the diploe and perforate the inner or outer table or both. Characteristically, there is no periosteal reaction as may be seen when the cortices of long bones are perforated. The granulomatous lesions may extend epidurally and may invade the brain. When the base of the skull is involved there is frequently destruction of the temporal bone on one or both sides and lesions in the mastoids and petrous portions of the bone are common. Otitis media is one

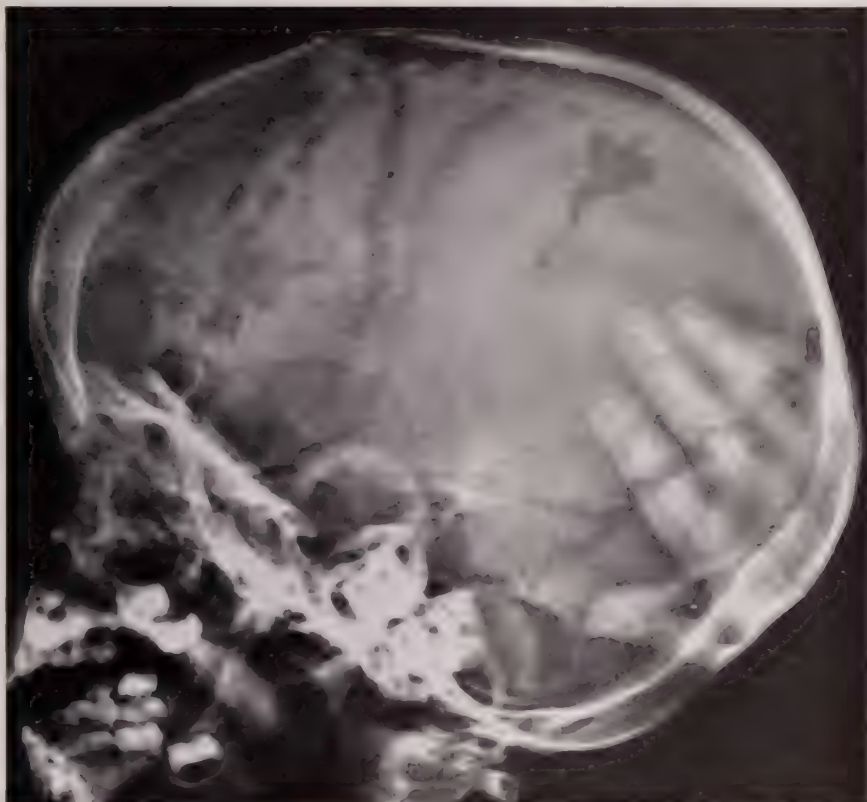


FIG. 10. *Letterer-Siwe Syndrome*. There are large, irregular and conglomerate areas of destruction in the frontal and parietal bones. In the frontal bone one of the smaller lesions has perforated the outer table.

of the most common presenting complaints in disseminated disease and is usually associated with demonstrable involvement of the temporal bone. Avery, *et al.* (11) found demonstrable changes in the temporal bone in three-fourths of their patients with otitis media. Lesions in the base of the skull may be seen without calvarial involvement. Destructive lesions of the sella turcica and sphenoid are less common and may or may not be associated with diabetes insipidus. Diabetes insipidus is generally considered to be due to involvement of the pituitary stalk or hypothalamus and is commonly present in the absence of any regional bone change. Exophthalmos is usually associated with lesions of the orbital bone

but small orbital lesions may be found without exophthalmos and exophthalmos may occur without demonstrable bony involvement.

Involvement of the mandible is common in Schüller-Christian syndrome and *the lesions characteristically begin around the apices of the teeth*. As these lesions expand they erode the lamina dura of the adjacent teeth and eventually destroy all the bone surrounding one or several teeth. This results in the com-

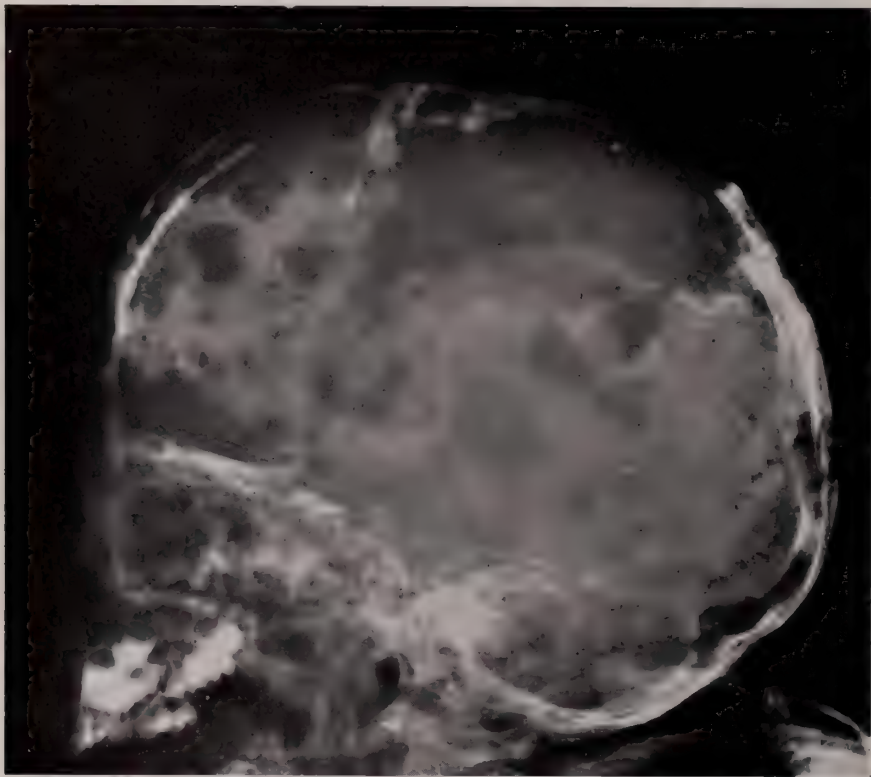


FIG. 11. *Schüller-Christian Syndrome*. Typical "geographic" pattern of destruction in the skull. The granulomatous lesions have extended beyond the confines of the diploic space and perforated both the inner and outer tables of the skull in several areas. There are destructive changes in the sphenoid. The patient had diabetes insipidus and draining ears.

plaint of "*loose teeth*" and gives rise to a roentgen appearance of "*floating teeth*" as the opaque teeth are surrounded by lucent granulomatous tissue (Fig. 13).

Lesions involving the ribs may be single or multiple or multiloculated. As they enlarge they tend to expand the bone, unlike the lesions of long bones. Involvement may be extensive, however, without expansion. Fractures through the involved portion of bone may occur.

Lesions of the pelvis are among the most common skeletal manifestations and most frequently involve the iliac bone. Most commonly they are situated just above the acetabulum and in our experience have tended to show reactive bone sclerosis particularly at their upper borders. Fig. 14 shows a characteristic

lesion. *Osteolytic lesions in the iliac bones of infants and children should strongly suggest histiocytosis X in one of its forms.* This is particularly true if the lesion has a well-defined margin and some *reactive osteosclerosis along its upper border.*



FIG. 12. *Schüller-Christian Syndrome.* This is the same patient shown in Fig. 11 after an eighteen month interval. There has been remarkable healing without osteosclerosis. The residual healing lesions have lost their well-defined margins. Most of the mandible has been destroyed and several remaining teeth appear to be floating in air. The discharge from the ears and diabetes insipidus continued.

The Spine

An interesting development relating to this disease complex has been the change in our concept of the etiology of *vertebra plana* (Calvé's disease). This condition is usually described as occurring in children up to the age of 15 years. It is characterized in its early phase by a lytic process in the vertebral body. The intervertebral disc spaces above and below the involved vertebra are normal or increased in width. Later the vertebral body collapses and shows increased density. Most often the collapsed body is wedge-shaped, being narrower

in its anterior portion. On some occasions it may be uniformly flattened presenting a "silver dollar" appearance. The pedicles on one or both sides may be partially destroyed (16). Usually only a single vertebra is affected. The condition was originally described by Calvé (17) in 1925 as an osteochondritis. Buchman (18) later suggested the term *vertebra plana*. For years it was considered to be due to an avascular necrosis similar to that seen in Legg-Perthes disease at the hips or Kohler's disease in the tarsal scaphoid. Although cases of xanthomatosis with involvement and collapse of a vertebral body were described by Jansson (19) in 1935 and by Davies (20) and Snapper (21) in 1948, no suggestion regarding a possible etiologic relationship between xanthomatosis and



FIG. 13. *Schüller-Christian Syndrome*. Most of the mandibular bone has been destroyed and replaced by granulomatous tissue. A few remaining teeth are surrounded by this soft tissue mass and have the roentgen appearance of "floating teeth."

the entity of Calvé's disease was offered. Brailsford (22) had also mentioned in his text book (1948) that he had seen this appearance of the vertebral bodies in cases with lesions in the skull typical of lipoid dystrophy and had noted that such spinal lesions may resolve. In 1951 Sir Thomas Fairbank, in his *Atlas of General Affections of the Skeleton*, stated that eosinophilic granuloma could cause collapse of a vertebral body, not unlike the appearance characteristic of Calvé's disease of the spine. In 1954 Compere and his associates (23) published four cases of Calvé's disease due to eosinophilic granuloma. Since then the impression has grown, supported by subsequent reports, that so-called idiopathic *vertebra plana* or Calvé's disease is, in fact, due to eosinophilic granuloma. While it is entirely possible that trauma or other factors may produce a similar picture, we are inclined to agree with Caffey (16) that it would be well to consider any instance of Calvé's disease as due to eosinophilic granuloma until

proved otherwise. In addition, since we now know that eosinophilic granuloma of bone may be multiple and that involvement of bone by granulomatous lesions may be only one expression of more disseminated disease, *the finding of Calvé's disease in the spine requires a roentgen skeletal survey to exclude the presence of other bone lesions* which may be silent. Furthermore, the chest should be



FIG. 14. *Eosinophilic Granuloma*. There are multiple well-circumscribed areas of destruction in the left iliac bone just above the acetabulum. Both the upper and lower borders of the involved area show bone sclerosis. The dimension of depth is apparent, especially in the lesion situated laterally.

examined to exclude pulmonary histiocytosis X and the patient should be observed for clinical evidence of disseminated histiocytosis X (*e. g.*, diabetes insipidus, skin lesions, etc.).

The spine is not among the more common sites of bone involvement in any of the forms of histiocytosis X but vertebral lesions may be seen in all three syndromes and are characterized by areas of destruction in the body which eventuate in collapse similar to that seen in so-called Calvé's disease (Fig. 15). Spontaneous healing and response to roentgen therapy is similar to that which may occur in the other bones.

NIEMANN-PICK DISEASE

Niemann-Pick disease like Gaucher's disease is considered to be a hereditary disorder of lipid metabolism. The condition is characterized by the accumulation of large pale vacuolated cells (presumably reticuloendothelial elements) in most organs but particularly in the liver, spleen and lymph nodes. The cells contain large amounts of phospholipid, especially the sphingomyelin fraction, and cholesterol which are localized primarily in the vacuoles. While in Niemann-Pick disease and Gaucher's disease the intracellular accumulation of sphingomyelin and cerebroside, respectively, is considered to represent the expression of a basic metabolic disorder, in histiocytosis X the current concept is that the granulomatous proliferation of histiocytes is primary and that the cholesterol lipidization of these cells is secondary.

Niemann-Pick disease is considered to be transmitted by an autosomal recessive gene. Not infrequently it may be found in siblings and it has appeared in a pair of identical twins. There is said to be some predilection for individuals of Jewish ancestry. Crocker and Farber (24) found thirty per cent of their eighteen patients to be of Jewish ancestry while Viedeback (25) found this group to represent fifty per cent of their cases. It is generally thought that this condition does not occur in Negroes but the case we have chosen for illustration (Figs. 16, 17) is a Negro infant of unmistakable ancestry.

Clinical manifestations may begin at birth but in most cases are first noted after the sixth month of life. In some cases, however, clinical evidence of the disease may not be noted until one and a half or two years of age and in rare late forms of the condition mild manifestations may arise first at around six years of age (24). The course is usually one of unremitting deterioration with death occurring within a few months but not all cases terminate so early. There is greater variation in duration than is commonly supposed. Crocker and Farber (24) have reported cases in which death occurred in the fourth, fifth, twelfth, fifteenth and nineteenth year. The commonest initial complaints are persistent jaundice, enlarging abdomen and poor general nutrition and development. When jaundice occurs it usually lasts for three or four months. Hepatomegaly usually precedes splenomegaly in contrast to the findings in Gaucher's disease. There may be moderate or considerable peripheral lymphadenopathy. Difficult feeding and vomiting may be prominent features. The skin often has a brownish

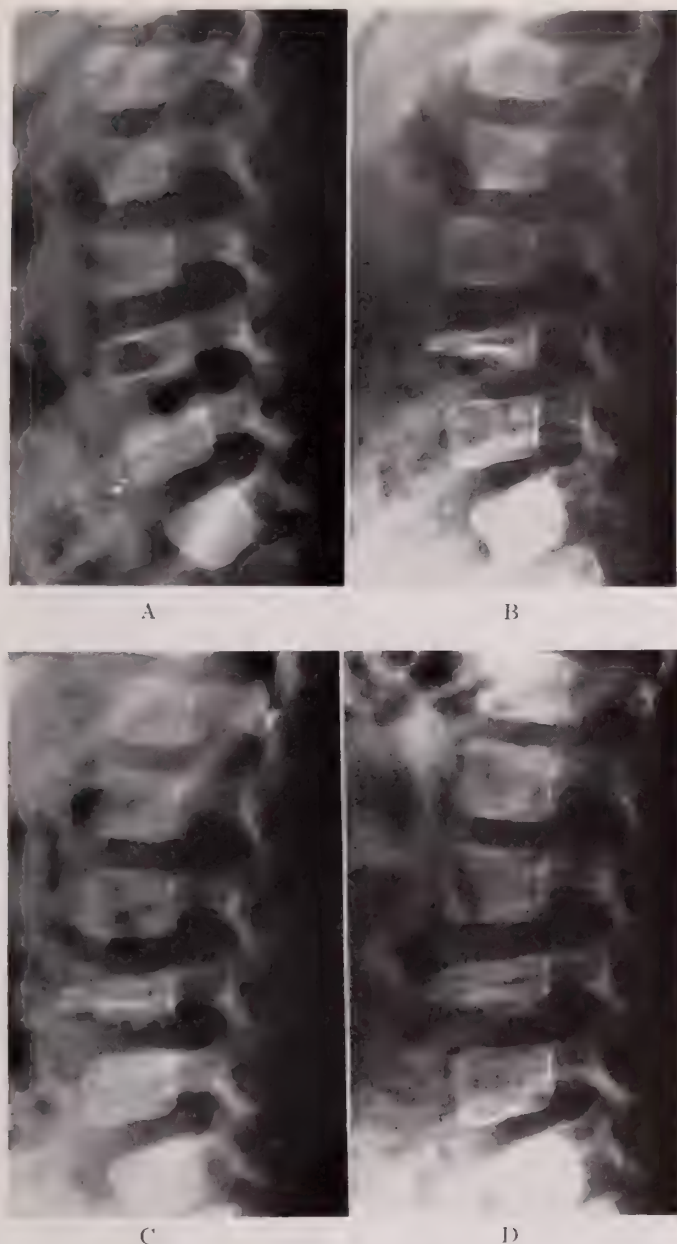


FIG. 15. *Eosinophilic Granuloma*. A.) There is partial destruction of the body of the fourth lumbar vertebra. The vertebral body is diminished in height. B.) Seven months later the vertebral body has collapsed into a wedge-shaped disc with increase in the density of the bone. Small areas of destruction are seen in the posterior portion of the body. The intervertebral disc spaces above and below the involved vertebra are increased. C.) Six months after B there is evidence of beginning restitution. The vertebral body has increased in height. D.) Nine months after (C) further regrowth is noted. The diagnosis was confirmed by biopsy. (Courtesy of Dr. Robert Freiburger, New York, N. Y.)



FIG. 16.

hue and cutaneous xanthomas are common. Cherry-red spots in the macular area of the ocular fundus, similar to those seen in Tay-Sachs disease, have been found in some cases. The incidence of this finding varies in different reports but probably is around 25 per cent. Pulmonary involvement is common. There is usually early serious central nervous system involvement with lipid deposits in the ganglion and neuroglia cells. Mental deterioration, nystagmus, blindness and motor disturbances are not uncommon.

There is usually moderate anemia. An important diagnostic feature is the presence of vacuoles in the cytoplasm of circulating lymphocytes and monocytes. Thrombocytopenia may be present in the later stages. Serum lipids are usually normal. Diagnosis is based on the clinical picture and demonstration of Niemann-Pick cells in marrow aspirates and lymph node biopsies.

Bone Changes in Niemann-Pick Disease

Although some infants may die before skeletal changes become apparent, roentgen evidence of bone involvement can be expected in many cases of Niemann-Pick disease. Some current texts deny the occurrence of demonstrable skeletal alterations and some clinical reports (26-28) refer to the bones as showing osteoporosis or osteomalacia. Crocker and Farber (24) found demonstrable bone change to be frequent in their series of 18 cases and Gildenhorn and Amromin (29) have recently reported a patient with rather marked changes. We have seen three cases of Niemann-Pick disease and in all three there was unmistakable roentgen evidence of bone involvement. The skeletal changes are due to the accumulation of large numbers of Niemann-Pick cells in the marrow. The medullary cavity is widened, the surviving trabeculae are coarsened, the cortices are thinned and there may be moderate failure of tubulation (Figs. 16, 17). Convexities of the contour such as are seen at the lower ends of the femora in Gaucher's disease, however, do not occur. Although Gildenhorn and Amromin claim this change in their case, the illustrations accompanying their report do not show it. The roentgen appearance is not specific and is similar to that seen in other marrow infiltrating diseases. The same pattern may be seen in the congenital hemolytic anemias, in infantile Hurler's syndrome and in Gaucher's disease before clubbing of the distal femora occurs. Significant skull changes have not been demonstrated and the short tubular bones of the hands and feet do not show changes which approach in degree the advanced alterations which are commonly seen in Cooley's anemia.

Two nonosseous roentgen findings in Niemann-Pick disease are worthy of mention. Reticulogranular infiltrations in the lungs are frequently demonstrable in roentgenograms of the chest. These are not distinctive and resemble pulmo-

Fig. 16. *Niemann-Pick Disease*. The bones of the lower extremities show marked osteoporosis. The marrow cavities are widened. The cortices are thinned. The patient was an 11 month old Negro female. Symptoms started at the age of three months with vomiting and feeding difficulties. Nutrition and development were poor. Generalized lymphadenopathy and hepatosplenomegaly were first recognized at ten months. There was slight nystagmus. Reticulogranular infiltrations were noted in both lungs. The peripheral blood showed vacuolization of monocytes. Bone marrow aspiration revealed typical Niemann-Pick cells. The pathology was confirmed by Dr. Carl Smith and Dr. Sadao Otani. Deterioration was rapid and the patient died at the age of fifteen months.

nary changes which occur in histiocytosis X and in infantile Gaucher's disease. Alexander (30) and Caffey (31) have described extensive calcification of the adrenal glands. In the cases described the calcified adrenals were enlarged. Alexander considered the enlargement to be due to abnormal lipid deposits in abundant vacuolated cells. Caffey interpreted the large size of the glands as an



FIG. 17. *Niemann-Pick Disease*. The short tubular bones of the hand are osteoporotic. The marrow cavities are widened and the cortices are extremely thin. The bones have retained their normal contours.

indication that calcification took place before birth or during the first days of life before physiologic neonatal atrophy of the adrenals had occurred.

GAUCHER'S DISEASE

Gaucher's disease is an uncommon, but not rare, hereditary metabolic disorder characterized by the accumulation of cerebroside in the reticuloendothelial system. Three substances have been isolated from tissues containing Gaucher cells. These are a galactosidocerebroside (kerasin), a glucosidocerebroside and a water-soluble glycolipid which has been called a "poly-cerebroside." The exact nature of the metabolic disorder involved in this disease is still not fully understood but it is generally considered that the defect is within the reticuloendothelial cells rather than in the intermediary lipid metabolism. Thannhauser (32) has suggested that there is an enzymatic disturbance within the reticulum cells which results in an increased synthesis of cerebroside and, at the same time, storage of these substances within the cells. The affected cells (Gaucher cells) are large round or polyhedral cells measuring 20 to 80 μ in diameter. They have one or more small, eccentrically placed nuclei. The cytoplasm is pale staining and has the appearance of wrinkled tissue paper. These cells do not divide by mitosis and degenerate slowly. Collections of Gaucher cells are found packed within the spleen, liver and bone marrow and, less often, within lymph nodes. In some cases the lungs and other organs may be involved.

Although the majority of reported cases have been in Jews, the disease may occur in other ethnic and national groups including Negroes and Orientals. The sex incidence is equal. Several members of the same family are often affected and rare cases involving more than one generation of a family have been reported. In most cases the condition appears to be transmitted by an autosomal recessive gene. Hsia, *et al.* (33), after a review of 110 affected families reported in the literature, concluded that Gaucher's disease may represent at least three genetically distinct groups: 1) in a few cases the condition is transmitted by an autosomal dominant gene; 2) in the majority the gene is transmitted as an autosomal recessive and 3) in a small group of cases with neurologic involvement in addition to the usual changes in bone, liver and spleen, transmission is also by an autosomal recessive gene.

Clinical Features

Acute Infantile Form. This form of the disease may begin within the first weeks or months of life. It pursues a rapid and malignant course and death usually occurs within a year or so. The infant is usually normal at birth but soon begins to show evidence of mental and physical retardation. There is progressive hepatosplenomegaly with enlargement of the abdomen and wasting of the extremities. Characteristic of the acute infantile form of the disease is severe neurologic involvement. Hypertonicity and opisthotonus are prominent features and choking spells, dysphagia, laryngeal spasm, cough, intermittent cyanosis and fever are often present. In contrast to the chronic form pulmonary involvement

is frequent, the alveolar walls, alveoli and bronchi often containing numerous Gaucher cells. Varying degrees of pancytopenia are usually present (34).

Chronic Form. The chronic so-called adult form of Gaucher's disease shows marked variability in regard to the age of onset and the rate of progression. This form of the disease has been found in patients ranging from infancy to old age. While the onset is considered to occur more commonly in patients under forty years of age a substantial number of cases are seen for the first time in patients between forty and seventy-nine years of age (35, 36). The onset is usually insidious and vague symptoms of weakness and easy fatiguability for long periods may precede the more objective findings of splenomegaly and hepatomegaly. Even when splenomegaly occurs it may be asymptomatic until relatively late in the disease so that an accurate estimation of the time of onset is difficult in most cases. Splenomegaly soon followed by hepatomegaly is usually the earliest finding and the one which brings the patient under medical care. It should be noted, however, that in occasional cases there may be no appreciable hepatomegaly or splenomegaly. In some such cases attention may be drawn to a spleen which appears slightly enlarged on radiographic examination of the abdomen but which cannot be palpated clinically. Lymphadenopathy is not a conspicuous feature. Pulmonary infiltration, although common in the acute infantile form, is infrequent in the chronic form. A yellow or patchy brown pigmentation, particularly on the exposed parts of the body, is a common finding. When this is fully developed on the lower extremities it characteristically extends from just below the knee to the instep and is usually symmetrical. In adults brownish wedge-shaped thickenings of the subconjunctival tissue (pingueculae) are frequent. The bases of these triangular-shaped areas are adjacent to the margins of the corneas and the apices are pointed to the inner or outer canthi. Mild to moderate anemia is common and there may be leukopenia and thrombocytopenia. Occasionally the anemia may be severe and may be the finding which calls attention to the disease. A complete pancytopenia may, in fact, eventually develop (37). Hemorrhagic episodes are common. There may be easy bruising of the skin from minor trauma, epistaxis or bleeding from the gums. Petechial hemorrhages may be noted but major hemorrhages are uncommon. Infiltration of the bone marrow by Gaucher cells may result in varying degrees of bone pain. In some instances this may be severe and localized. Under these circumstances the condition may be mistaken for osteomyelitis (38-41). According to Strickland (42) when cases of Gaucher's disease are mistakenly operated upon for osteomyelitis a sinus may form which is intractable and may persist for many weeks or months.

Diagnosis is confirmed by the finding of Gaucher cells in the bone marrow, spleen or liver. These cells are not demonstrated in the peripheral blood nor are the blood findings in any way characteristic of the disease. Liver function tests are usually normal. Tuchman, *et al.* (43) have provided some laboratory aid by finding that the serum acid phosphatase may be elevated. They examined the serum of eight patients with proved Gaucher's disease and found the acid phosphatase elevated in all of them. The patients ranged in age from 5½ years to 75 years. Five were males and three were females.

While there is no cure for Gaucher's disease splenectomy has been found to be effective in relieving symptoms due to the pressure of an enlarged spleen and in correcting the blood dyscrasias associated with hypersplenism.

Bone Changes in Gaucher's Disease

The incidence of radiographically demonstrable bone changes in Gaucher's disease is not known. Some patients of all ages may fail to show any roentgen evidence of bone involvement, others may show only minimal bone change and in still others the skeleton may be the site of extensive and advanced alterations. The roentgen appearance of the bones is, after all, dependent on the degree and extent of marrow infiltration by Gaucher cells and presumably, on associated degenerative and reparative processes. In some cases the Gaucher cell infiltration is predominantly visceral, involving primarily the spleen and liver with only minimal or no demonstrable osseous change. In others the skeleton is a major site of infiltration and demonstrable bone changes are outstanding. Cases occur, however, in which neither visceral nor osseous changes are prominent or in which, conversely, both are prominent. It is apparent, therefore, that the pathologic expressions of this disease show marked variability.

As the rare form of acute infantile disease characteristically runs a rapid progressive course ending in early death bone changes are seldom seen. When the chronic form of the disease begins in infancy the first changes are usually found at the lower ends of the femora where Gaucher cell proliferation destroys many of the bony trabeculae, widens the medullary cavity and thins the cortices. As the disease progresses this process involves the other large tubular bones resulting in an appearance similar to that seen in some cases of Niemann-Pick disease and bearing a strong resemblance to the findings in the congenital hemolytic anemias. It is usually possible to differentiate this appearance from that seen in severe thalassemia major by examination of the hands and feet. In both Niemann-Pick disease and Gaucher's disease the short tubular bones of the hands and feet are, at best, only mildly or moderately affected. In Cooley's anemia, on the other hand, the short tubular bones are usually the most severely involved portions of the skeleton at this early age. It may be difficult or impossible, however, to differentiate these reticuloendothelioses from sickle cell anemia for when sickle cell disease shows evidence of diffuse marrow hyperplasia in infancy or early childhood the hands and feet do not usually show changes commensurate in degree with those found in Cooley's anemia. With increasing age the destructive changes in the shafts in Gaucher's disease may be spotty and the rarefaction may not have the uniformity seen in Niemann-Pick disease.

Despite the continued progress of the disease process most patients with the chronic form of Gaucher's disease experience very little disability and continue in a relatively satisfactory state of health for long periods. For this reason it is usually difficult to determine the time of onset of the condition or to obtain frequent follow-up roentgen studies of the bones. As a result there have been very few studies of the evolution of the bone changes in this disease and such studies have been practically confined to the lower ends of the femora.

Probably the earliest and most consistent change is found at the distal ends

of the femora where the bone shows generalized porosis. As the Gaucher cell proliferation continues there is usually an expansion of the lower ends of these bones (Fischer's sign). An important feature of this bone change is that *the normal concavity of the contour is first lost along the medial border of the bone* (Fig. 18). This border at first straightens and then becomes convex. In many cases the lateral border will retain some degree of concavity or will only later become convex. The adjacent cortices show thinning and this thinning is also first apparent on the medial side. The contour of the bone becomes club-shaped and has been described as having an "Erlenmeyer flask" appearance. This feature, although common, has perhaps been stressed too much since *advanced changes may occur in the femora without this contour deformity*. In addition, the deformity may be limited to one femur, the other retaining a normal contour.

Expansion of bone is a common feature of Gaucher's disease and is by no means confined to the lower ends of the femora. The upper ends of the tibiae and the humeri often have a swollen appearance and localized areas of spongiosal destruction may be associated with regional expansion giving the bone an irregular contour.

As the disease progresses destruction of bony trabeculae may be spotty or diffuse. According to Pick (44) there is marked variation in the collections of Gaucher cells in the individual bones. In some cases they are diffusely scattered, in others they form poorly circumscribed confluent foci or they may collect in small nests or isolated groups. These findings are consistent with the variation in the roentgen appearance.

Long segments of the bone medulla may show thinning and destruction of the trabeculae and atrophy of the cortex and the involved segment may be rather sharply delimited from the adjacent normal bone (Fig. 19). In addition to the cortical atrophy the inner aspect of the cortex is often scalloped at localized areas of increased resorption. There may or may not be expansion of the bone at the affected sites. In some cases the involved area is more or less homogeneously rarefied but there may be coarse or fine reticulation of the lesion by surviving trabeculae. When the reticulation is coarse the appearance is that of honeycombing and is *similar to the honeycomb pattern of myelomatosis* (Fig. 20). As in myelomatosis the axillary border of the scapula and the outer end of the clavicle may also be involved and the resemblance may be striking. This combination of localizations is not as frequently seen in Gaucher's disease, however, and often the Gaucher lesions show some associated sclerotic change which aids in differentiation.

Smaller areas of rarefaction may be poorly or sharply circumscribed and vary considerably in size and shape. Commonly they are elliptical, their long axis running parallel to the long axis of the shaft. Occasionally they may have peripheral borders of increased density (Fig. 21).

Early descriptions denied the occurrence of periosteal changes in Gaucher's disease but this feature, although uncommon, does occur. The periosteal reaction may have a lacelike pattern or may be of the "layer" type (Fig. 19). Strickland (42) has described cases showing both patterns. It is interesting that in his case



FIG. 18.



FIG. 19.

FIG. 18. *Gaucher's Disease*. The lower end of the right femur shows a loss of its normal contour. The medial border of the bone is slightly convex. The lateral border still maintains some concavity. The cortices are thinned and the trabecular pattern of the spongiosa is greatly reduced. The patient was a thirty-two year old Jewish female whose sister also had Gaucher's disease.

FIG. 19. *Gaucher's Disease*. The upper three-fourths of the left tibia shows diffuse destruction of the spongiosa. The infiltrated area is sharply delimited from the normal bone at the lower end of the shaft. The cortices in the involved area are thinned and there are multiple areas of scalloping due to localized increased resorption. There is also an extensive area of marrow infiltration in the fibula. The destruction in this bone is somewhat more irregular. The medial fibular cortex is thinned and scalloped. Along the medial aspect of the upper fibula there is a lace-like periosteal reaction. There is a fine reticulation of the involved area in the midshaft. Several small poorly defined areas of destruction can be seen at the lower ends of the bones. The patient was a 71 year old Russian-born male. At the age of 65, prior to a contemplated rectal operation, he was found to be suffering from a severe anemia. Bone marrow aspiration at that time revealed Gaucher cells. This examination was made six years later because of severe pain and swelling of both lower legs. There were no known relatives with splenomegaly.

showing the "layer" type reaction the lesion occurred on the inner aspect of the distal tibiae in the absence of any demonstrable alterations of the adjacent bone. This is similar to the change we have described in myelosclerosis. Periosteal reaction may occur, however, adjacent to involved bone. Unlike the periosteal



FIG. 20. *Gaucher's Disease*. There is coarse reticulation of the infiltrated marrow of the right humerus producing a honeycomb pattern. Smaller localized areas of destruction are seen in the proximal terminal spongiosa. Linear and irregular areas of destruction associated with sclerosis are noted in the axillary border of the scapula and there are medullary lesions in the outer end of the clavicle with scalloping of the regional cortex.

changes seen in histiocytosis X the periosteal lesions in Gaucher's disease *usually* occur over a radiographically intact cortex except where pathological fracture has occurred. Levine and Solis-Cohen (45) have reported an exception to this rule, however. It is important to recognize that periosteal elevation may occur in Gaucher's disease because destructive areas associated with sclerosis and periosteal reaction have been frequently misdiagnosed as osteomyelitis in patients with localized pain and swelling.

Pathological fractures through areas of demonstrable involvement are not

unusual. These tend to occur most frequently in the vertebrae and the weight bearing long bones. Interestingly enough, however, spontaneous fractures may occur at sites where the bone appears normal on roentgen examination. Pre-



FIG. 21. *Gaucher's Disease*. There are numerous small scattered areas of destruction at the lower ends of the radius and ulna. The long axis of most of these is parallel to the long axis of the shaft. The medial cortices at the distal ends of both bones are thinned and slightly convexed with localized expansion of the bone contour. A small elliptical rarefaction at the distal end of the radius has a periphery of increased density. Minimal scalloping of the cortices of both bones along the length of the shaft can be seen. At the upper end of the radius there is a honeycomb pattern.

sumably the Gaucher cell infiltration at these sites, although weakening the bone, has not been sufficient to produce gross changes detectable radiographically.

Osteosclerosis is a major feature of many cases of Gaucher's disease. It is

not ordinarily an early finding, however. In some cases new bone is laid down around and between areas of bone destruction or may develop along the inner aspect of the cortex in areas where there is evidence of a destructive process



FIG. 22. *Gaucher's Disease.* Both femora are the sites of diffuse destructive and sclerotic changes. In the upper ends of the bones there are confluent areas of diffuse and localized destruction. In these regions the cortices are not thinned but they are scalloped along their inner margins. Lower and adjacent to these areas the cortices are thickened by the deposition of new bone along their inner aspects. This narrows the medullary cavities within which areas of destruction are being replaced by bone. At the distal third of the right femur the medial cortex has become convex and thinned. The distal third of the left femur has maintained a normal contour despite extensive involvement. The medial cortex in the middle third of the left femur is split.

(Fig. 22). The thickening of the cortex narrows the medullary cavity in a fashion similar to that seen in sickle cell disease, myelosclerosis or Paget's disease. Areas of radiolucency may eventually be replaced by bone. Usually the appearance is one of combined destruction and osteosclerosis but in many cases one or

the other may predominate (Figs. 23, 24). An odd feature, commonly seen, is splitting of the cortex (Figs. 22, 25, 26). Long layers of bone may develop in the medullary cavity parallel to the cortex but separated from it by a thin line of lucency. This is sometimes referred to as a "bone within bone" appearance.



FIG. 23. *Gaucher's Disease*. The lower portion of the femur is mottled by numerous irregular areas of sclerosis. The lesions are predominantly osteosclerotic and the appearance bears a striking resemblance to that seen in myelosclerosis.

Windholz and Foster (48) described these as "bone cylinders." They are also commonly seen in sickle cell disease. In some cases areas of sclerosis have developed in bone without any preceding evidence of destruction (48). It is assumed that they replaced areas of Gaucher cell proliferation which produced no roentgen signs.

The pathogenesis of osteosclerosis in Gaucher's disease is a controversial

aspect of the subject. Pick (44) has described delicate connective tissue and reticulum fibers which course between the Gaucher cells often intimately fused with the periphery of the cell. When the Gaucher cells degenerate and become necrotic this intercellular fibrous network thickens. It is considered by some that direct osseous metaplasia of these fibers accounts for the osteosclerosis seen radiographically. Gordon (49), however, considers the sclerosis to be a reparative process secondary to destruction.



FIG. 24. *Gaucher's Disease*. This is the same patient shown in Fig. 25. There are mixed destructive and sclerotic changes in the upper humerus. The lesions are predominantly sclerotic. The pattern here also resembles myelosclerosis. This was the first roentgen examination of a sixty-four year old male whose complaint was easy fatiguability and hepatosplenomegaly. The duration of the disease could not be determined. The patient's brother also had Gaucher's disease.

Proliferation of Gaucher cells in the femoral heads with subsequent collapse is a common occurrence in Gaucher's disease (Fig. 27). Less often similar changes occur in the heads of the humeri. The process may be unilateral or bilateral. It may occur at any age. In children it may be indistinguishable from Legg-Perthes disease or any of the numerous conditions associated with aseptic necrosis of the femoral heads. If there are associated Gaucher changes in the shaft the diagnosis is readily made. Otherwise, the nature of the lesion may be entirely unsuspected until clinical findings are evaluated. Reconstitution of the collapsed bone is rare but Arkin and Schein (51) have reported the case of a 10 year old girl in whom almost complete restitution of the femoral head took

place after prolonged relief from weight bearing. In the adult the appearance may simulate sickle cell disease, osteoarthritis, caisson disease or old trauma. The lesion has no characteristic features but additional lesions should be looked for in the femoral neck and shaft.



FIG. 25.



FIG. 26.

FIG. 25. *Gaucher's Disease*. Lateral view of the femur shows splitting of the anterior cortex in the lower part of the bone adjacent to an area of diffuse sclerosis.

FIG. 26. *Gaucher's Disease*. The lower end of the left femur is club-shaped. The medullary cavity is widened and the lower cortices are thinned. This is more marked at the medial cortex which is slightly convexed. The medullary lesions are predominantly osteosclerotic. The lateral cortex is split.

Changes similar to those described in the long bones may occasionally be seen in the short tubular bones of the hands and feet. The most minimal findings in these bones consist of scalloping of the inner aspect of the cortices. Circumscribed areas of rarefaction with or without associated sclerosis may also be seen and in some cases the lesions may be predominantly sclerotic.



FIG. 27. *Gaucher's Disease*. There is destruction and collapse of the femoral head. Minimal sclerotic changes are noted in the femoral neck and intertrochanteric region. The trabeculae at the ischial tuberosity are atrophied and the cortices are thinned. There is an area of sclerosis in the iliac bone adjacent to the inferior portion of the sacro-iliac joint. Sclerotic changes are also noted at the symphysis pubis. Sclerotic and destructive changes may be seen at the symphysis in the absence of any pelvic or hip lesions.

The flat bones may also be the sites of demonstrable bone change. Occasionally lesions in the mandible are outstanding. They typically take the form of unilocular cystlike lucencies, usually surrounding the apices of the teeth but without involvement of the peridental membrane. In some cases there is merely a diffuse osteoporosis. Rib and pelvic lesions are relatively uncommon. The question of whether the skull may show roentgen changes in Gaucher's disease is an in-

interesting one. Some authors have stated categorically that demonstrable changes in the skull do not occur in this condition. Others have referred to the findings as inconclusive. In a few instances a fine punctate porosis has been described (42, 46) and there are rare reports of small isolated radiolucencies (47). It is our impression that both types of change do occasionally occur. The mottled porosis, sometimes localized, is usually not striking, however, and the small areas of lucency may be considered to be vascular (Fig. 28). Until gross, incontrovertible lesions are demonstrated or correlated roentgen-pathological studies are

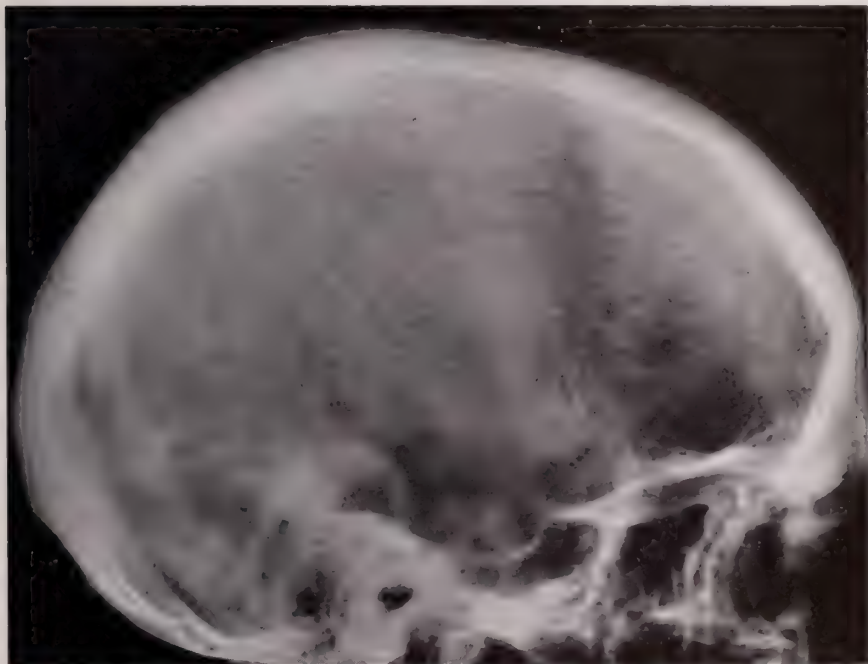


FIG. 28. *Gaucher's Disease?* This is the skull of a patient whose long bones were the sites of extensive involvement by Gaucher's disease. There are numerous small localized areas of radiolucency in the parietal bone. In the frontal bone there is a poorly defined area of mottled osteoporosis. This examination was part of a skeletal survey. The patient was not available later for more detailed roentgen study. These findings are not considered conclusive.

made, the subject will probably continue to be controversial. Pick (44) has described collections of Gaucher cells in the diploic marrow which would lead one to expect roentgen changes, at least in some cases, but it is natural to assume that if demonstrable alterations are considered not to occur in the skull, this part will not often be subjected to roentgen examination. A similar situation existed for some time in regard to myeloid sclerosis and some of the recent literature still repeats the old contention that skull changes do not occur in that disease. Yet it has been well demonstrated that they do.

Because osteoporosis of the spine is common in so many conditions it is important to remember that Gaucher cell infiltration of the vertebrae may pro-

duce a similar appearance. *Gaucher's disease must be included in the differential diagnosis of vertebral osteoporosis.* Any stage of the process may be seen and the appearance may be that of diffuse demineralization, demineralization with cupping or eventually with collapse of one or more vertebrae. In advanced cases



FIG. 29. *Gaucher's Disease.* There is marked osteoporosis of the dorsal vertebrae. Three vertebral bodies are collapsed to the shape of silver dollars. The intervertebral disc spaces are not involved. There is a gibbus deformity at the level of the two lower collapsed bodies. Some cupping of the porotic vertebrae is noted.

there may be gibbus deformity (Fig. 29). Snapper and Goldberg (50) have alerted us to the fact that rare cases of Gaucher's disease may occur in which there are no characteristic bone lesions but in which there is a generalized resorption of bone. Such cases occurring in the older age groups are often passed over as post-menopausal or senile osteoporosis since the chief complaint may be back pain and only the spine is examined. As we have pointed out in the discussion of myelomatosis there are several conditions in which a nonspecific demineralization of the spine may be an outstanding feature. Included among these are myelomatosis, hyperparathyroidism, leukemia, hemoglobinopathies, steroid effect, osteomalacia, and Cushing's disease. In some such cases, while the spine may be demineralized other portions of the skeleton may show more characteristic lesions or may fail to show demineralization indicating that the bone change is limited to the central skeleton. Errors in diagnosis can be reduced if roentgen skeletal surveys are made in all cases of osteoporosis of the spine. Sometimes, although certain conditions may be eliminated, it still will not be possible to make a radiologic diagnosis but the attending physician can be alerted to the possible clinical diagnoses which should be considered.

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THE EDUCATIONAL CHALLENGE TO VOLUNTARY HOSPITALS*

WILLARD C. RAPPLEYE, M.D.†

The topic for discussion should be considered in the broad context of the health problems of the country. Adequate health services are one of the primary needs of the American people. They are now third among U. S. industries in numbers of persons employed and rank in importance with other major public concerns such as housing, transportation, employment, education and social security, with each of which they are associated. The idea of comprehensive medical services for the entire population as a basic social right of every individual is a recent development in the United States. The objective of the health services in the aggregate is to meet that obligation and of education to build opportunities for the training of the personnel necessary to meet that objective successfully.

Medical security is coming in some form and it is up to the professions to propose the ways and means by which sound progressive plans can be formulated. It would indeed be shortsighted and, in the long run, futile to ignore the broad social implications involved. At the moment the purely economic factors are being overemphasized. The important concern should be with the competence of the professional services rendered. The public in the last analysis will see that the supply of doctors will be maintained although the level of competence, if unguided, may be lower than present day scientific knowledge would indicate as desirable. The continuation of a high quality of physicians, the recruitment of superior students and competent faculties in competition with other fields of endeavor will depend upon those who see clearly the thread of educational needs throughout the career of the physician. The problem of providing proper medical services is not alone that of producing more physicians but of educating them better and obtaining a more satisfactory distribution and effective utilization of existing doctors and future graduates. The solution is in part the creation and financial support of hospital centers which should be the base of operation of modern medical services.

This generation is experiencing a major explosion of scientific knowledge and of demand for trained workers. The greatest handicap the nation faces is an acute undersupply of high level skills which now represents a bottleneck in the national economy. The obligations of medical education in modern society are as diversified as the functions it must perform and the objectives it must serve.

The public is turning to the educational institutions, hospitals and the health professions to propose and guide the programs designed to safeguard human resources. Medical education broadly conceived is the keystone in the entire arch of health services, the expenditures for which now total over \$27 billion a year. Provisions for the basic operation of the 85 medical schools are less than one per cent of that total, an insignificant proportion in relation to the vital

† President, Josiah Macy, Jr. Foundation, New York.

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contributions which those institutions make to the welfare of individuals and the nation.

Preparation for the profession of medicine is no longer limited to the usual four-year medical course and internship. It now embraces the entire spectrum of predoctoral and postdoctoral training in the medical schools and in the teaching and community hospitals, a span of professional education often reaching eight or more years. The number of individuals in the later stages of training now exceed the total of the predoctoral undergraduate medical students.

An aspect of the expanding graduate programs is the growth of hospital residencies, the number of which has increased by 600 per cent in the last twenty years. They now total 31,733 in the approved institutions alone, between four and five times the number of American medical graduates each year. During that period the number of American medical graduates has risen 35 per cent. The many responsibilities and demands for competent instructional staffs for the educational guidance of the large numbers of trainees in the hospitals, who often need more individual attention than the predoctoral student, and for the continuation education of the medical and other professional practitioners are very heavy.

Every hospital, voluntary or municipal, should be concerned with the professional education of doctors, dentists, nurses, social workers, technicians of every kind, young attending physicians, administrators and the general public. Fortunately, an increasing number of non-university institutions now have or are creating modern laboratories and other facilities and professional staffs of excellence, some of them with a nucleus of full-time members, which are able to provide a high quality of instruction to house staffs and practicing physicians and to strengthen patient care.

The advancement of knowledge in the health sciences is an essential function of medical education. The gap between what is known and what is applied is widening and probably will continue to do so. A major national problem is to devise methods of making available promptly to the sick and handicapped, and those apparently in normal health as well, the benefits of new knowledge regarding the diagnosis, treatment and prevention of disease and disability. One of the primary responsibilities of medical education at all levels, therefore, is to translate the new discoveries into the preparation of personnel whose duty is to apply that knowledge to the needs of patients and the community.

In response to the public conviction that support of medical research is an investment in better health the Congress has appropriated large sums of money for that purpose during recent years. The total annual expenditures for medical research through the Federal Department of Health, Education, and Welfare have risen from \$3 million in 1946 to \$442 million in 1961. They now represent over one-half of the total expenditures in the country for that purpose. Approximately 27.5 of the \$442 million were spent in 1961 through the National Institutes of Health for extramural programs, of which amount \$148 million was in grants to medical schools for research projects, including \$13 million for clinical centers,

and \$55 million for traineeships and fellowships. The total of \$203 million exceeds the annual expenditures for the basic operations of the 85 schools. Another \$50 million went to hospitals and other institutions for medical research programs and \$22 million for construction of research facilities. The expenditures authorized by the N.I.H. for extramural research projects, training grants and research facilities for 1962 are 40 per cent over those in 1961, roughly \$385 million. President Kennedy's recommended budget expenditures for fiscal 1963 are nearly 70 per cent greater than the amounts spent in 1961. A large part of these appropriations have been made to institutions with facilities and investigators in a position to carry out the programs proposed.

The voluntary health agencies continue to collect about \$200 million a year, a considerable part of which is devoted to research. Philanthropic foundations and individuals give large support for scientific studies. In New York City the Health Research Institute has become a substantial grantor of local research funds. The National Fund for Medical Education, the United Health Foundations and the American Medical Education and Research Foundation are several other agencies assisting in different ways in the promotion of medical research and education.

The large amounts of money now provided from governmental and other sources for research emphasize the shortage of facilities in the medical schools and hospitals and focus particularly upon the urgent need of sufficient numbers of properly qualified individuals to carry forward the investigations. The effect of large grants and research funds upon all aspects of medical education—faculty, students, curriculum, facilities and upon the very nature of the inquiries themselves, is a matter of growing concern. The solution to the situation is not the curtailment of research activities but of expanding and strengthening the teaching functions of the schools and hospitals if the full potential of the investment by the Government in research and postdoctoral training is to be realized. Abundant physical facilities, adequate scholarship, traineeship and fellowship funds and even unlimited financing of investigation will become largely academic questions in the long run unless the recruitment and preparation of competent practitioners, teachers, investigators and hospital staffs and the improvement of medical instruction of undergraduate medical students, postdoctoral trainees, hospital residents, paramedical personnel and practitioners can be accomplished.

A new approach is altering the functions and responsibilities of universities, hospitals and medical schools. The new developments are a part of the revolution of rising expectations so far as health services are concerned and are creating new organizational patterns and administrative procedures. One well recognized evidence of the trend is the concept of the hospital center. In such developments the hospital assumes heavy educational and financial burdens in addition to those of patient care alone. They include the support of residents, teaching ward services, special outpatient clinics, laboratories, rooms for instruction, offices, extra nursing procedures, maintenance of facilities, more ancillary personnel and enlarged administrative expenses.

CONTINUATION EDUCATION OF PHYSICIANS

The continuation education of physicians in practice aimed to keep them abreast of new developments in science, clinical medicine and the prevention of disease and disability is one of the essential features of any national plan of medical services. It offers special opportunities for community as well as teaching hospitals to contribute to the solution of the problems. The new Joint Committee on Continuation Education comprising representatives of nine national agencies will make its report shortly.

One feature of this problem has always been the difficulty of providing satisfactory learning opportunities for the busy practitioner. Even in the most attractive inducements there is great difficulty in reaching the physician who is unable to leave his daily duties to go to teaching centers. Hundreds of "courses" are offered and publicized by medical schools, hospitals, professional associations, academies and others but they reach only a small proportion of the practicing doctors. The challenge in all of these efforts is the motivation of the physician to continue his learning and in some manner to provide opportunity for his active participation in the postgraduate educational process rather than be in a passive role in attendance at lectures and demonstrations or in merely reading publications.

Probably the crux of this whole situation is that the undergraduate medical course increasingly is placing emphasis upon "learning" by the student as distinguished from "teaching" by the faculty, a focus on the "how" rather than the "what" to learn. Only through the permanent development and acquisition of sound methods and habits of study by the undergraduate medical student or intern will the future physician be able to continue his own professional development. Hence the success of graduate medical education depends in considerable measure on the extent to which undergraduate medical schools fulfill those functions.

LENGTH OF MEDICAL COURSE

Several medical schools for different reasons are undertaking to shorten the combined premedical and medical course from the usual eight year period to six years. This is in response to the conviction of some that the overall preparation for medicine can safely be shortened, partly in view of the long postdoctoral hospital periods that are now required. This device has been tried in the past in this country but was abandoned several decades ago. It may prove successful in certain instances under the new conditions that pertain.

It is also of interest that a small number of universities are initiating programs for two-year medical schools. Several of these are intended ultimately to be expanded to full four-year schools. There is still active discussion of the creation of a few such plans focussed more particularly on what has been discussed as "Schools of the Life Sciences" or "Schools of Human Biology." In such endeavors some of the students completing the two-year program may transfer to the third year of a regular four-year medical school.

THE SUPPLY OF PHYSICIANS

The necessity for an increase in the output of physicians for the future needs of the country is generally accepted although too little attention is being paid to questions regarding more effective utilization than at present of the existing profession and the future additions that will be made to it. This is partly a matter of the distribution of doctors, governed so largely by the patterns of medical practice, economic considerations, public education, population shifts and many other factors. A number of the major communities have more physicians now than are required if their services were effectively and efficiently utilized. Other areas of the country are, or soon will be, in short supply. All of these and similar questions have a direct bearing on the problems of the community and teaching hospitals.

There is a fundamental socio-economic-professional shift now in process relative to how physicians in the future will conduct their practices, how they will be organized and how their services will be financed. There are now about 133 million persons (over 70 per cent of the population) covered by voluntary prepayment hospital "insurance," 121 million by surgical expense "insurance" and close to 90 million with some degree of coverage for medical expense services through prepayment. The total with "major medical expense insurance" is now over 31 million. A considerable segment of the population is provided with health services from tax sources through welfare, hospital and health departments. These are significant trends which are likely to continue, particularly as state, municipal and Federal programs, labor union-industry plans and local community organizations for medical care grow.

If progress can be made in the better utilization and management of medical facilities, resources and personnel through functionally structured hospital services, ambulatory care, laboratory services, home care, nursing homes, public infirmaries and group practice that would increase the efficiency of health care by even five to ten per cent, which is quite conservative, the results in savings of medical manpower would be equivalent to the output of ten new medical schools. Changes in the methods of practice and the increased "productivity" of the modern physician through the growth of paramedical services and various other devices have an important bearing on the numbers of physicians needed for the country in the future and particularly point to the importance of greater utilization of their highly developed skills, knowledge and judgments.

During the last forty years the number of physicians has increased 117 per cent while the population has risen 76 per cent. During the last decade the enrollment of medical schools has risen 22.8 per cent while the population has increased 16.4 per cent. The number of medical graduates from American schools was 6,994 in 1961 compared with 2,529 in 1922. The first year class of 1960-61 is 8,298. In 1960 there were 8,030 additions to the medical profession, including 1,569 graduates of foreign medical schools. Fifteen new schools have been created since 1943, nine since World War II and eight more are now proceeding with their plans.

The recruitment of medical students in the future will depend more upon the challenges which medicine will offer for satisfying careers in science, graduate education, clinical opportunities and public service to well qualified and properly motivated college students than upon scholarships or other financial aid, important as they are. Strengthening professional career opportunities will be the greatest single incentive in the recruitment of medical students and future physicians.

About 19 per cent of physicians licensed to practice in the country last year were graduates of foreign medical schools. Some of the foreign medical graduates are well trained and competent. Many of the others have high intelligence and eagerness to be taught but the large majority of them now coming into the United States have a preparation well below the standards of general and professional education which are regarded as satisfactory. Large numbers of are employed as interns or residents in hospitals which offer little in the way of educational opportunities. Much of the program for foreign medical graduates remains unsatisfactory and, from an international point of view, unfortunate.

The most logical solution to the staffing of American hospitals, voluntary and municipal, not offering sufficient educational opportunities for approval is the employment by the hospitals of well qualified physicians on a full-time or part-time basis. The younger men and women can remain in the positions for several years while they are getting established in the community. This in part would solve the difficult period between the completion of residency training or military service and the start of practice. About 25 per cent of recent medical graduates in practice are now on a full-time salary basis. Two-thirds of the American residents at present in the hospitals are desirous of remaining in some form of organized practice when they complete their programs.

Probably one of the most important defects in the whole scheme of medical education is the wastage of talent and competence at the end of the hospital residency when many young men and women in that stage of development cannot easily be absorbed into the present structure of medical practice. Under existing conditions there is no well established bridge from the hospital period of preparation to establishment in practice although this is being solved in part through the slow development of various forms of group practice and salaried medical services, often in hospitals.

What is needed is a clearer definition and recognition of the stream of medical education and more clearly defined opportunities to which a medical student may look forward as he completes the successive phases of his professional preparation and moves upward toward full professional responsibility in present day practice. There should be an established program which permits a recent graduate to start in a hospital, group practice or other medical organization in which he is employed and trained and retained later as a staff member or be prepared, as in other professions or walks of life, to move to other established positions. Obviously some of this flow of young medical men is channeled now but proper organization of such a program could render great assistance to the national medical services and would enhance opportunities for recent medical graduates.

NEED FOR COORDINATION OF EFFORTS

There is urgent need for coordination of the many multi-professional, social, economic, welfare and political programs now so conspicuous by their fragmentation, splintering, duplication, ineffectiveness and skyrocketing costs. New patterns for the distribution of health services, better organization and utilization of facilities and personnel, regionalization of activities, new forms of private and governmental cooperation, and a new approach to the joint financing of the educational and community services are urgently needed. These are acute problems, particularly in the face of such developing national plans as those for the medical care for the aged either under the Kerr-Mills Act or the proposed King-Anderson (Kennedy) bill under the Social Security System, and with local proposals concerning the staffing of municipal hospitals, the relocation of facilities, the cooperation of voluntary hospitals with public institutions, the joint activities of the Departments of Hospitals, Health and Welfare and the improvement of nursing homes, proprietary hospitals and home care, under consideration.

LOCAL PROBLEMS

Growing out of some of the general considerations presented there are certain special problems in New York City. One is that of the recruitment and supply of house staffs in both voluntary and municipal hospitals. About 48 per cent of those positions are now occupied by graduates of foreign medical schools. Another is the fact that one-third of the physicians has no hospital affiliation. The announced plans for increasing proprietary hospitals are a challenge.

The question of establishing one or more new medical schools in the New York area is under wide discussion and being studied by a committee appointed by Mayor Wagner. There are 191 physicians per 100,000 population in New York State, compared with 132 per 100,000 in the country (e.g. 182 in Massachusetts, 161 in California and 127 in Illinois). In New York City there is a ratio of about one doctor to 478 persons (national average of one to 757 and one to 420 in Manhattan, Queens and The Bronx). Put in another way and with necessary interpretations, if New York had a supply comparable to the national average the number of physicians in the City would be about 10,000. The actual number is over 16,000. On the basis of the present and probable future supply of doctors locally there is not a good argument for a new medical school in New York City.

Some have suggested that another school in New York City is indicated on the grounds that local students have difficulties in securing admission to medical schools. The number from New York State enrolled as first year medical students in American medical schools, however, is 6.8 per 100,000 of the population compared with the national figure of 4.6 per 100,000. It is surpassed in this regard only by Nebraska (7.2) and Washington, D. C. (7.7). In New York State 6.5 students per 1,000 persons at age 20 receive a medical education in American medical schools compared with a national average of 4.2 per 1,000.

Some have urged the building of new medical schools as a means of supplying house staffs and visiting physicians for hospitals not affiliated with medical schools. There are better and more economical ways of dealing with that problem.

New York City has a large number of scattered voluntary and municipal hospital facilities not now fully utilized for medical teaching and research which might be made available under proper educational direction and leadership to increase the supply of doctors and other health personnel for the country. They can and do serve in varying degrees as opportunities for clinical clerkships, internships, residencies and other postdoctoral training, providing adequate educational supervision and guidance can be supplied. A modern medical school requires more than clinical facilities and groups of excellent practicing physicians in the community although their availability might encourage the creation of hospital medical schools with or without the umbrella of an educational institution qualified to supply the necessary leadership. The crucial factors in establishing a satisfactory medical school are the assurance of a competent faculty dedicated to academic medicine, the support of a strong university, sufficient laboratory and clinical facilities under the control of the faculty, necessary ancillary personnel and stable financial resources.

The probable future shortage of physicians in the country as a whole may form the basis for urging another medical school in New York City as a contribution to the national needs in view of its great hospital, educational and professional resources, possibly to be financed in part by Federal and State funds. The Mayor's Committee is currently studying the whole question. It is well known that every medical school wherever situated is in fact a national institution since it educates physicians and other health personnel who later locate in all parts of the nation as teachers, investigators or practitioners.

In meeting health problems the university as a vital social agency must share with hospitals public responsibilities of a most demanding character, often of a nature not entirely academic. The combination of university and hospital in a joint organization under educational guidance represents one of the outstanding contributions of this era, a type of administrative structure that is assuming a greater role in medical exploration and professional education at all levels. The hospital or medical center represents the most satisfactory vehicle for providing modern health services to patients, families and the community and for channeling aid in the educational and research programs from governmental and private sources. Results will depend to a considerable degree upon the willingness and ability of educational institutions to assume genuine leadership and guidance and of voluntary and other hospitals to amplify their traditional functions of private and ward patient care to include real educational objectives. No city in the country is as well endowed with the material, scientific and educational resources as New York. There are many excellent programs at the student, internship, residency and postdoctoral levels, some affiliated with and others independent of the medical schools and universities. The opportunities for even greater contributions present a challenge of the first magnitude.

STUDIES IN MYASTHENIA GRAVIS

EVALUATION OF CARDIAC CONDUCTION

PETER KORNFELD, M.D., AND KERMIT E. OSSERMAN, M.D.

New York, N. Y.

Sudden unexplained death has always challenged the clinical acumen of the physician treating the patient with myasthenia gravis. Respiratory paralysis or anoxia due to obstruction has been presumed to be the cause of these deaths, but cardiac conduction disturbances have never been ruled out. Since the heart is delicately controlled by the autonomic nervous system, it is of interest to consider what effect, if any, myasthenia gravis has on cardiac conduction. The following experiment is an attempt to evaluate the influence of myasthenia gravis upon the cardiac conduction mechanisms.

METHODS

Sixty patients ranging in age from 15 to 40 years were used in this study. Thirty were normal control subjects (15 females, 15 males) and thirty were myasthenic patients (21 females, 9 males) comprising all the clinical classifications of myasthenia gravis except neonatal (1). None of the myasthenics had any clinical evidence of thymic enlargement. Both groups were matched as to age, however, as noted above, there was a larger number of female patients in the myasthenics. All sixty participants were free of any form of cardiovascular, pulmonary, hematologic or thyroid abnormalities. Every participant had a normal twelve lead electrocardiogram recorded and a normal two-meter posterior-anterior chest roentgenograph taken.

Throughout the study, the following procedures were performed: a standard lead II was recorded and measurements taken of the heart rate, PR, QRS and QT intervals to determine any changes in rate, rhythm or conduction.

1. Unilateral carotid sinus pressure was applied for ten seconds to determine vagal sensitivity. The right carotid sinus was massaged first; if it was found to be sensitive no further massage was performed at this stage. If insensitive, the left side was similarly massaged. If both sinuses were found to be insensitive, bilateral eye-ball pressure was applied. During this procedure, if the heart rate slowed by less than ten per cent, the patient's carotid sinus was considered to be insensitive.
2. After a suitable interval, each candidate was challenged with a rapid intravenous injection of 20 mg of edrophonium (Tensilon) chloride.
3. After ten minutes, by which time the drug effect had completely disappeared, the patient received another rapid injection of 20 mg of edrophonium chloride, followed by a ten-second carotid sinus massage.
4. After the patient's pulse had returned to the baseline rate and remained

From the Myasthenia Gravis Clinic and The Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

stable for approximately five minutes, 0.4 mg of atropine sulfate was quickly injected intravenously.

The recordings of the electrocardiogram taken during this entire procedure were then analyzed.

RESULTS

Measurements of various components of the electrocardiograms recorded are shown in the Table I. Since cardiac arrest is a rare occurrence, the table

TABLE I
Electrocardiograph Analysis

	Control Subjects (30)		Myasthenic Patients (30)	
	Mean	Range	Mean	Range
<i>Baseline:</i>				
Heart Rate.....	78	66-100	77	68-96
P-R Interval (sec.).....	0.17	0.12-0.21	0.16	0.10-0.20
QRS Duration (sec.).....	0.07	0.05-0.10	0.07	0.05-0.10
QT Duration (sec.).....	0.36	0.32-0.40	0.37	0.35-0.40
<i>After injection of edrophonium chloride:</i>				
Heart Rate.....	71	56-88	69	58-86
P-R Interval (sec.).....	0.17	0.13-0.20	0.17	0.13-0.20
QRS Duration (sec.).....	0.07	0.05-0.10	0.07	0.05-0.10
QT Duration (sec.).....	0.36	0.32-0.40	0.37	0.35-0.40
<i>After injection of edrophonium and carotid sinus pressure:</i>				
Heart Rate.....	64	50-80	61	50-76
P-R Interval (sec.).....	0.17	0.13-0.21	0.17	0.14-0.21
QRS Duration (sec.).....	0.07	0.05-0.10	0.07	0.05-0.10
QT Duration (sec.).....	0.36	0.33-0.40	0.37	0.35-0.40
<i>After injection of atropine sulfate:</i>				
Heart Rate.....	92	82-110	95	82-116
P-R Interval (sec.).....	0.16	0.13-0.20	0.16	0.11-0.20
QRS Duration (sec.).....	0.07	0.05-0.09	0.07	0.05-0.10
QT Duration (sec.).....	0.36	0.32-0.39	0.36	0.35-0.40

includes not only average figures but extremes of range. Carotid sinus stimulation caused slowing of the heart rate by 10 per cent or more in 27 of 30 control individuals and in 28 of 30 myasthenic patients. Fourteen control subjects and 8 myasthenic patients complained of mild muscarinic side effects such as lacrimation, salivation or abdominal cramps following the injection of edrophonium chloride. All these effects were dissipated within three minutes after an injection of edrophonium chloride. An intravenous injection of atropine sulfate produced a subjective awareness of palpitations in some patients. Electrocardiograms recorded occasional auricular extrasystoles in three control subjects and in two myasthenic patients. The onset and duration of action of edrophonium chloride and of atropine sulfate were similar in both groups.

Edrophonium chloride effects were noted within 30 to 55 seconds after injection and its clinical action completely disappeared within four minutes. Clinically, atropine sulfate produced apparent manifestations within 25 to 40 seconds after injection; but did not reach its peak action for 8 to 10 minutes. No slowing of the heart rate was observed following intravenous injection of atropine sulfate, as has been reported by some authors (2, 3).

Measurement of heart rate, PR, QRS and QT intervals, as influenced by the various procedures outlined, revealed that the myasthenic patient reacts to vagal stimuli in the same qualitative and quantitative manner as does the non-myasthenic individual. In this study, the degree of severity and the duration of myasthenic symptoms had no apparent influence in the cardiac conduction mechanism.

DISCUSSION

At postmortem examination, patchy myocardial necrosis has been found to be a lesion seen at times in the heart of a myasthenic patient (4). By means of the immunofluorescent antibody fixing technique (5) it has been demonstrated that the myasthenic globulin fixes the myosin of striated and cardiac muscle of both the normal and the myasthenic (6). As yet, immunologic involvement of the Purkinje system has not been shown. Others in the literature have commented on the increased incidence of tachycardia and vasomotor instability encountered in myasthenia gravis (7). Thévenard's advocacy of carotid sinus denervation as an ameliorating procedure for this disease strengthened the clinical impression that vagal tone may be abnormal in many of these myasthenic patients (8).

This study, which excluded from both groups all patients in the "coronary age range," confirmed the previously reported work of Taquini *et al.*, that the vagus nerve exerts its normal control on the heart of the myasthenic (9). Although the recorded electrocardiographic response to edrophonium chloride, carotid sinus massage and a combination of the two was slightly more marked in the myasthenic, this was statistically insignificant. Following an injection of atropine sulfate, transient flattening of some T waves, shortening of the PR interval and an increase in the heart rate were observed in both the myasthenic and control groups. No other recorded electrocardiographic abnormalities were seen in either group. This confirmed the results seen through routine electrocardiography performed on over 500 myasthenic patients, seen in the past ten years. However, nonspecific ST and T wave changes, although minor, were observed in five young myasthenics free of any other illness. No correlation could be found among the degree of severity, duration of the myasthenic syndrome and the reaction of the heart to vagal or vagolytic stimuli.

It should be pointed out that the myasthenic patients used in this study were ambulatory and did not have the extra burden of being in any form of crisis. Thus, two significant factors were missing, namely the lack of any degree of anoxia and elevation of arterial $p\text{CO}_2$ which are present, to some extent, in crisis. It is well known that anoxia and CO_2 retention increase cardiac irritability

and are often associated with a sudden outpouring of catecholamines. The additional administration of atropine sulfate or of anticholinesterase compounds, under these circumstances, may be responsible for a physiologic type of death. In a series of 500 patients, twelve had cardiac arrest despite tracheostomy, aspiration and clinically apparent adequate ventilation with mechanical assistance. These twelve patients were subjected to immediate open or closed chest cardiac massage and defibrillatory procedures which resulted in return to life for periods of one to thirty days for 9 patients. Three patients are still alive. Postmortem examinations in this group revealed a high incidence of pulmonary infection. The myocardium showed only an irregular incidence of pulmonary atelectasis, though of varying degree, as well as focal or confluent pulmonary infection, an irregular incidence of nonspecific patchy necrosis. No pathology was found in the central nervous system.

It is possible that the tests used in this study were not subtle enough to bring out any alterations in the cardiac conduction mechanism which might have been precipitated by superimposed anoxia or CO_2 retention. The danger of oxygen deprivation or CO_2 retention to the myasthenic patient was felt to preclude the addition of any anoxemia test to this protocol.

SUMMARY

In response to vagal and vagolytic stimuli, the reaction of the heart of a myasthenic is qualitatively and quantitatively similar to the nonmyasthenic patient. The absence of any degree of anoxia or CO_2 retention on the cardiac conduction mechanism may be the reason why this study failed to reveal any changes in the cardiac status of the ambulatory, controlled myasthenic patient.

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UREMIC PERICARDITIS AND TAMPONADE IN A TEN YEAR OLD GIRL

HOWARD R. RAPPAPORT, M.D.

New York, N. Y.

Uremic pericarditis is usually described as a dry, fibrinous pericarditis (1). It is a frequent occurrence in both acute and chronic renal failure (2), and has been noted since the original report of Bright in 1836 (3). More recent studies have indicated that there is usually some effusion (1, 2, 4) but this is rarely large enough to produce cardiac tamponade (5). The case report presented here is of interest because of the occurrence of tamponade due to uremic pericarditis in a young child.

CASE REPORT

C.S., a ten year old white female, was first admitted to The Mount Sinai Hospital on February 5, 1960. She was transferred from another institution where the diagnosis of chronic nephritis with uremia had been established. The patient was given a high fat, high carbohydrate, low protein diet, with calcium and vitamin K supplementation. Antibiotic therapy was begun. Initial blood chemistry values along with a representative sampling of the laboratory tests carried out during this hospitalization are presented in Table I. The electrocardiogram obtained on admission is shown in Figure 1.

On February 13, following a blood transfusion, the patient's temperature rose abruptly and she complained of upper abdominal pain. The fever and pain decreased after acetylsalicylic acid and diphenhydramine hydrochloride administration. The following day the temperature again rose abruptly. The patient later complained of chest pain and a pericardial friction rub became audible (Fig. 2). Roentgen examination the next day demonstrated a heart of normal size (Fig. 3a). The pericardial friction rub became less intense during the following three days. On February 23, a kidney biopsy was obtained and conventional microscope examination revealed fibrosis of almost all glomerulae and some polymorphonuclear infiltration consistent with chronic glomerulonephritis and secondary pyelonephritis.

On February 26, the patient became short of breath and the blood pressure fell to 100/60. The heart was now percussed to the anterior axillary line and the sounds were poorly heard. The liver was palpable two centimeters below the right costal margin. Roentgen examination showed small bilateral pleural effusions with massive cardiac enlargement and loss of detail suggesting pericardial effusion (Fig. 3b). Fifty milliliters of bloody fluid that failed to clot were obtained by pericardiocentesis. The removal of this small amount of fluid produced symptomatic relief. On February 29, increasing dyspnea made necessary another

From the Department of Pediatrics, The Mount Sinai Hospital, New York, N. Y.

pericardial tap productive of 240 cc of bloody fluid that again failed to clot. On March 2, a third pericardiocentesis was performed with removal of 300 cc of bloody fluid. Following this procedure x-ray examination showed a slight reduction in the size of the cardiac shadow. On March 4, the patient was digitalized.

TABLE I

Representative sampling of blood chemistry values obtained during hospitalization.

Date	BUN mg%	CO ₂ meq/L	Cl meq/L	Na meq/L	K meq/L	Ca mg%	P mg%	A/G gm%	Uric acid mg%	Creat. mg%
2/5	148	17.3	91	136	4.2	7.4	7.0	2.9/2.8	11.5	13.2
3/4	132	11.8	84	133	4.3					14.4
3/10	100	11.6	95	128	4.9	7.1	5.6			10.2
3/30	106	25.8	97	141	7.6	9.6				8.0
4/11	142	19.4	100	133	6.6	9.0	5.4	2.8/2.7	8.7	10.2
4/19	168	13.9	91	137	8.1	8.9	7.0			14.7
4/26	245	12.8	92	133	7.4	8.5	9.2			11.6

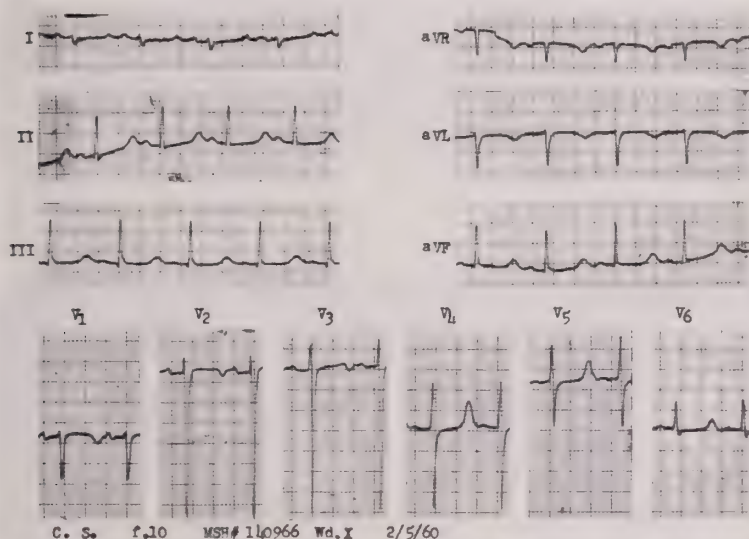


FIG. 1. Electrocardiogram taken on admission. Note prolonged Q-T interval reflecting hypocalcemia.

During the next week there was considerable improvement with further reduction in the cardiac silhouette on x-ray (Fig. 3c).

On March 26, when the blood pressure was 206/160, the patient had a grand mal convulsion. During the next month and a half, the child had progressive renal failure and hypertensive encephalopathy that became refractory to treatment. The patient died on May 2, 1960, slightly less than four months after her initial hospitalization and two and one half months after the onset of pericarditis.

DISCUSSION

Bright, in describing the clinical features of chronic glomerulonephritis, stated that patients with this condition were prone to sudden attacks of pericarditis (3). Pericarditis occurs in both acute and chronic renal failure (2), but the

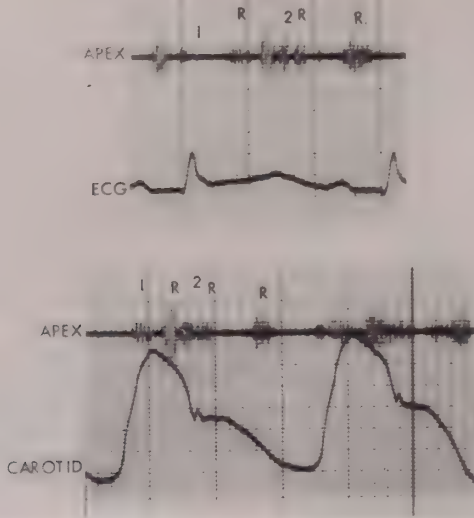


FIG. 2. Phonocardiogram of friction rub with systolic, early diastolic and presystolic components.

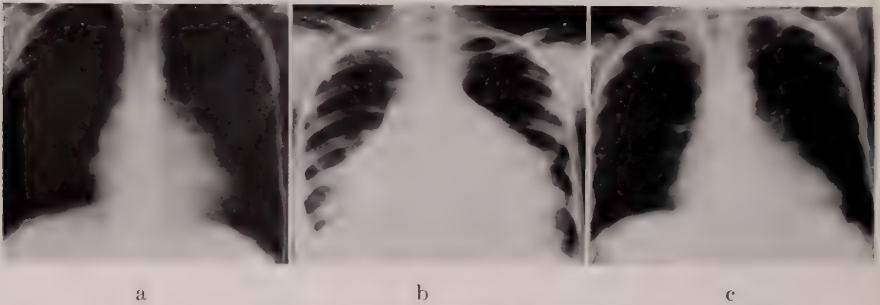


FIG. 3a. P-A chest x-ray demonstrating the normal size of the heart.

3b. Note now the massive enlargement of the cardiac silhouette and the small bilateral pleural effusions.

3c. The heart shadow in this subsequent examination has returned toward normal.

incidence and significance of the pericarditis in each are quite different. In acute renal failure, Wacker and Merrill reported that 18 per cent developed pericarditis and that slightly more than half of these patients died (2). In chronic renal failure, the reported incidence of pericarditis has varied widely (1, 2, 4, 6) but it seems likely that it lies close to 50 per cent. The appearance of a pericardial

friction rub is an ominous sign and death follows in one to three weeks. Survival is rare beyond two months (1, 2, 4, 5).

The etiology of uremic pericarditis is uncertain. Bacteria have been cultured from the pericardial fluid occasionally, but these have usually been considered secondary invaders. There has rarely been an inflammatory reaction to confirm the presence of infection (1, 4). A chemical basis for the etiology, while attractive, also has little support. Clinically the occurrence of pericarditis cannot be correlated with the level of BUN (2). In animals, azotemia, produced by injection of urea or by inducing renal failure, is not accompanied by pericardial inflammation (4). A third theory suggests "irritation" from products of muscle necrosis. While changes in muscle fibers with some mononuclear infiltration are occasionally seen, these changes are not seen consistently in the presence of pericarditis (1, 4).

Effusion is a frequent companion to uremic pericarditis. About half the cases of uremic pericarditis have 100-300 cc of fluid and another 10-25 per cent have over 400 cc of fluid (1, 4, 7, 8). The larger effusions are often bloody, possibly due to the general hemorrhagic tendency in uremia (7) or to the rupture of blood vessels in the organizing pericarditis which are torn by the increasing effusion (8). Tamponade is rare and has not been previously reported in a child (5).

Clinically, pericarditis is associated with a friction rub in about $\frac{3}{4}$ of the cases (1, 4). One half of these have, in addition, pain or precordial oppression of varying degree (1, 2). The patients are usually hypertensive and are often in congestive heart failure with some cardiac enlargement. With increasing effusion the cardiac size increases though the rub may remain even with large effusions (1). The diagnosis of an effusion large enough to produce cardiac embarrassment is not difficult. There is evidence of severe right-sided failure with edema, distended neck veins, and a positive hepatojugular reflux. The heart sounds are distant. The electrocardiogram shows complexes of low voltage and the x-ray examination confirms the presence of fluid in the pericardium. The degree of cardiac embarrassment is more a function of the speed of fluid accumulation than of the quantity. The presence of fluid first produces an elevation in the end diastolic pressure of the right ventricle and right atrium due to mechanical compression. There is secondarily an inflow stasis with obstruction to right atrial and ventricular filling and a fall in cardiac output. Finally a fall in mean arterial blood pressure occurs (9).

The treatment is pericardiocentesis by needle or indwelling catheter (10). Removal of small amounts of fluid may be beneficial, as the case reported here illustrates. While this may produce temporary relief, the course of the primary disease remains unaltered.

SUMMARY

A case of uremic pericarditis with tamponade is described. Pericarditis in chronic glomerulonephritis is again noted to be an ominous sign. Uremic peri-

carditis usually has an associated small effusion. Tamponade is rare. The diagnosis and treatment of cardiac tamponade are discussed.

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Clinico-Pathological Conference

HYPERTENSIVE CARDIOVASCULAR DISEASE WITH DIABETES IN AN ALCOHOLIC PATIENT

Edited by
FENTON SCHAFFNER, M.D.

New York, N. Y.

A 49 year old white male was admitted to The Mount Sinai Hospital for the first time after he had fainted, fallen, and cut his head. There was a deep cut in the right parietal area which bled profusely. He had vomited, become dizzy and was incoherent for a short while following the episode. Several days prior to admission the patient noted dizziness on standing. He had been taking chlorpromazine tablets occasionally.

The patient was a known diabetic although he had never received treatment. There was a long history of alcoholism and enlargement of the liver had been found previously. The patient had been treated with guanethidine and reserpine for hypertension. Five months prior to admission a left lumbar sympathectomy had been performed because of severe claudication in both lower extremities. Two months later, he had a myocardial infarction with severe congestive heart failure; he was digitalized and placed on maintenance digoxin. Pneumonia of the right lower lobe of the lung followed; there was an uneventful recovery. There had been multiple episodes of pneumonia during the past years.

The temperature was normal, pulse 108 min, and blood pressure 160/110. The patient appeared plethoric. He could not stand. His speech was slightly garbled. Reflexes were normal. Although the cut was deep, the bone was intact. There was a presystolic gallop with no cardiomegaly. A₂ was greater than P₂. A firm, nontender liver edge could be felt four fingerbreadths below the costal margin. The spleen tip was questionably palpable.

The urine contained 3+ albumin and 2+ sugar. A few white cells and finely granular casts were seen. Hemoglobin was 13.1 Gm%, white blood count 20,500/mm³ with 86% polymorphonuclear leukocytes, 18% of which were band forms. BUN was 23 mg%, blood sugar 166 mg%, serum albumin 3.4 Gm%, globulin 3.3 Gm%, bilirubin 1.4 mg%, cholesterol 310 mg%, transaminase 54 units, cephalin flocculation 1+, and sedimentation rate 60 mm/hr. Skull x-rays were normal. Electrocardiogram showed a sinus tachycardia, a right bundle branch block pattern with a QRS of 0.13 sec. The ST segment was depressed in V₂-5.

The laceration was sutured without difficulty. His blood pressure varied from 120/80 to 210/140 at bed rest. Urine sugar varied from 0-3+ with most fasting specimens negative. Guanethidine, reserpine and benzdyrolflumethiazide were started again on the third hospital day. His temperature went to 102° on that

From the Department of Pathology, The Mount Sinai Hospital, New York, N. Y.

day but the next morning he was normotensive and his white blood count dropped to 11,100/mm³. Later in the morning he became unconscious and convulsed. At this time he was pulseless and cyanotic. Electrocardiogram revealed ventricular fibrillation. External defibrillation was accomplished with 250 volts but the heart failed to respond to the external pacemaker, and despite external massage, intravenous levarterenol and calcium chloride, he died.

*Dr. Max Ellenberg**: Despite this sketchy history, we can see that there was multisystem involvement. This man had cardiac disease, peripheral vascular disease, hypertension, and pulmonary, hepatic and renal involvement. There was considerable drug intake, and chronic alcoholism. It is no surprise that this man had diabetes. I would like to try to tie everything into one package, with diabetes as the wrapping paper and ribbon.

The incidence and severity of diabetic complications are not necessarily related to the severity of the carbohydrate metabolic disorder. Although these complications are often directly proportionate to the duration of the diabetes, they may occur independently, and serve as the initial clinical manifestation, before the appearance of overt carbohydrate metabolic disturbance. This man obviously had mild diabetes that required no treatment. As far as we know, it existed for at most two or three years. Nevertheless, the possibility or potential for more severe complications was present.

We know that he had a myocardial infarction and had been in failure on at least two occasions. We can assume that he had myocardial disease on the basis of coronary arteriosclerosis with coronary occlusion and myocardial infarction.

He had hypercholesterolemia; it has been said for years that diabetics tend to have a higher elevation of cholesterol than the nondiabetic population. However, uncomplicated diabetes without renal disease and in moderately good control statistically is not associated with a serum cholesterol level that is higher than the nondiabetic state. We shall return to the hypercholesterolemia.

The patient had peripheral vascular disease, and intermittent claudication which required a lumbar sympathectomy. We have no record of his pulses nor whether they were palpable so we cannot determine the level of arterial involvement. I have never seen any beneficial results from a lumbar sympathectomy in peripheral vascular disease on an arteriosclerotic basis in a diabetic patient. There are good reasons for this: first, there is usually diabetic neuropathy already; second, the rigid, sclerotic vessels do not have a capacity to respond. If I were to predict the pathological findings, I would say that a man with severe heart disease and intermittent claudication most probably had atherosclerosis of the aorta and marked involvement of the larger vessels.

It is difficult to explain from the available information why there were recurrent pneumonias. One always thinks of some form of bronchial stenosis, but there is no evidence of that here. Tuberculosis must be considered in the diabetic patient, but this man had mild diabetes, he had never been in coma, and he ap-

* Assistant Attending Physician, The Mount Sinai Hospital, New York.

peared plethoric. Moreover, a diabetic under reasonably good control is no more susceptible to infection than the nondiabetic.

Multiple myeloma must be considered in view of the albuminuria. In multiple myeloma there is frequently associated proteinuria with a tendency toward infection. The latter is often marked by recurrent episodes of pneumonitis. The patient's serum globulin was not greatly elevated, which makes multiple myeloma a less likely possibility.

We are left with pulmonary infarction, which immediately suggests itself in a man with severe vascular disease, who had a coronary occlusion two months prior to hospitalization, followed by right lower lobe pneumonia. There was probably previous congestive failure with pneumonia, which again suggests infarction. I would guess that the results at autopsy included repeated pulmonary infarctions.

An interesting symptom is the dizziness on standing. This suggests orthostatic hypotension. There are two possible explanations. First, this man was receiving various antihypertensive preparations. The day before his accident he had taken chlorpromazine. He may have had drug-induced orthostatic hypotension. Second, the more interesting possibility is that he had orthostatic hypotension on the basis of diabetic autonomic neuropathy. This is not very rare in diabetes with neuropathy, although there is usually other evidence of peripheral or autonomic neuropathy. Although the protocol states that this patient had normal reflexes, I would say that the odds are even that he had absent deep tendon reflexes, specifically absent ankle jerks. The pathologist will not be able to decide the cause for orthostatic hypotension but it is important to know that it is not a rare phenomenon with diabetic neuropathy and autonomic nervous system involvement.

In an episode of hypotension, the patient fell. While his other episodes were relatively mild, this one was dramatically different in that he fell and sustained a severe head injury. In addition to the laceration, he was dizzy, he vomited, was incoherent and had garbled speech. I think it was due to something other than orthostatic hypotension. We know that he died in an episode of ventricular fibrillation. He may have fallen because he had a transitory episode of some ectopic paroxysmal tachycardia at that moment. If this were due to a coronary occlusion, he could have the nidus for an infarct which resulted in his death three days later, again, with paroxysmal tachycardia. This would be the only good explanation for the transaminase elevation. It would also account for the leukocytosis, which was not striking, and would help to explain the elevated sedimentation rate. His electrocardiogram showed a right bundle branch block with depressions of the ST segment in the precordial leads V2-5. This may have represented a change from a previous ECG indicating that this man probably had a coronary artery occlusion with myocardial infarction. On the other hand, if this were an old pattern, then I could find consolation in the fact that we know that with a right bundle branch block acute ECG changes may be obscured. Also, since this man was on digitalis, the ST depressions in V2-5 may have been due to the drug.

Nevertheless, I think that this man had the beginning of his demise at the

moment he fell and sustained his scalp laceration and cerebral injury, and that it was in the form of a beginning coronary occlusion and myocardial infarction with transitory paroxysmal ectopic arrhythmia.

It is difficult to include a four-fingered liver in the realm of diabetes. In a man who is a known chronic alcoholic, the odds are good that he has Laennec's cirrhosis. In any diabetic, even a mild one, who has been untreated, the incidence of one to two finger hepatomegaly is very common. Furthermore, although there is still a great deal of disagreement on this point, the literature recently has tended to point to the fact that cirrhosis in the diabetic is more common than in the nondiabetic. Even though I feel that this man has alcoholic cirrhosis, which basically is unrelated to diabetes, I think there is a diabetic component to the hepatomegaly.

We have to mention the possibility of amyloid because he had severe albuminuria and an enlarged liver. I am willing to discard it because there is no other evidence for amyloid. In this secondary type of amyloidosis with renal and hepatic involvement, one ordinarily expects some underlying reason for it which I cannot discern from the available evidence.

What I have saved for last probably had no direct relationship to his exitus, although I think it is important from the clinical point of view and equally so from the pathologic point of view. I refer to the renal aspects of diabetes. This man had 3+ albuminuria. In spite of relatively massive albuminuria, there is a relative paucity of formed elements. This is characteristic of diabetic nephropathy. Some of the albuminuria might have been a result of dehydration or the severe stress reaction he had with the fall. However, for purposes of discussion, I am assuming that the 3+ albuminuria was real and that he had had it for a reasonably prolonged period of time.

The rather unfortunate euphemistic term, "diabetic nephropathy," has come into being almost as a form of self-defense because there is no specific single lesion that one finds in a diabetic kidney at autopsy. All diabetics have arterial and arteriolar involvement; they usually have pyelonephritis, and they may or may not have glomerular involvement in the form of glomerulosclerosis. It is any combination of or all three factors that is included in the term, "diabetic nephropathy."

No simple, clear-cut, recognizable clinical picture can be consistently or repeatedly related to any specific pathological picture. Confusion arises from the fact that the eponym "Kimmelstiel-Wilson" has been used to describe on the one hand a clinical syndrome of nephrosis, albuminuria, azotemia, hypertension, retinopathy, and neuropathy clinically, and on the other, the nodular lesion of intercapillary glomerulosclerosis. We must separate the two since one is a clinical description, the other a pathological description.

One reason why there has been such a clinical-pathological discrepancy is that so many of these people have congestive heart failure with edema in addition to their renal involvement. This is too often clinically interpreted as part of a nephrotic syndrome. Many patients also have albuminuria, part or all of which may be a result of congestive heart failure and congestion of the kidney.

In this case we are a little more fortunate. The patient did not have a nephrotic syndrome but we also know that he did not have congestive heart failure despite the history of failure on at least two occasions. He had a presystolic gallop which usually means failure. On the other hand he had a right bundle branch block so I shall interpret the presystolic gallop as an adventitious third sound as heard in bundle branch block. A2 was greater than P2; there were no rales or distended neck veins; there was no tenderness of the liver or any hepatojugular reflux and no peripheral edema. Nevertheless, he had massive albuminuria which therefore must be renal in origin. He had hypertension and beginning azotemia. Even though he did not have nephrosis from the edema point of view, if I may be permitted to stretch a point, chemically he had a beginning nephrotic syndrome. He had, for example, hypercholesterolemia. He did not have an elevated globulin or a reversed albumin globulin ratio, but the globulin is sufficiently elevated to let me assume that he had a moderate abnormality. Had he lived long enough, I am reasonably sure this man would have developed edema.

Because of the severe albuminuria, the paucity of formed elements, the associated hypertension and the elevated BUN, I think that he had a specific diabetic lesion which at autopsy will be glomerulosclerosis, in addition to the obvious vascular involvement of the kidney.

Glomerulosclerosis also poses a problem because there are two kinds: diffuse glomerulosclerosis and the specific intercapillary glomerulosclerosis (the nodular lesion of Kimmelstiel-Wilson) which, incidentally, is the only pathognomonic pathological lesion of diabetes.

Experience has shown that there is a much higher degree of correlation between the nephrotic syndrome and diffuse glomerulosclerosis rather than between the nephrotic syndrome and the nodular lesion of Kimmelstiel-Wilson. Since this man did not have edema, I am going to guess that the dominant lesion in the kidney was the nodular lesion of Kimmelstiel-Wilson or intercapillary glomerulosclerosis.

To summarize, I think this man had myocardial infarctions, old and new, with more than one coronary artery occlusion; evidences of old pulmonary infarctions, possibly with a new one; alcoholic cirrhosis of the liver with some fatty infiltration which I would like put on a diabetic basis; and diabetic nephropathy with severe arteriolar involvement and involvement of the renal glomeruli, probably most conspicuously intercapillary glomerulosclerosis (*i.e.* the nodular lesion of Kimmelstiel-Wilson).

*Dr. Willy Mautner**: What about the hypertension?

Dr. Ellenberg: The hypertension could be one of two things. He could have had associated essential hypertension which is more common in diabetics than nondiabetics, or it could be due to the renal and vascular involvement associated with diabetes.

Dr. Mautner: I want to thank Dr. Ellenberg not only for an excellent discussion but also for a great deal of fortitude in discussing a case with an insufficient history and limited investigation. The patient came in with what was thought

* Assistant Attending Pathologist, The Mount Sinai Hospital, New York.

to be a myocardial infarct, was handled gingerly, and died before any thorough study could be done.

The heart was markedly enlarged, weighing 680 grams. The thickened wall of the left ventricle showed a moderate degree of diffuse fibrosis. The right side was markedly dilated and also showed some degree of hypertrophy. In the posterior wall of the left ventricle, there was a myocardial infarct extending from the endocardium through about one-half the thickness of the ventricular wall. A fair degree of fibrosis along the edge of the infarct indicates that it must have occurred at least a few days before death. The coronary arteries, as expected, showed severe arteriosclerosis.

The lungs were markedly congested and on section showed alternating areas of emphysema and atelectasis. Many alveoli contained pigment-laden macrophages as seen in chronic passive congestion.

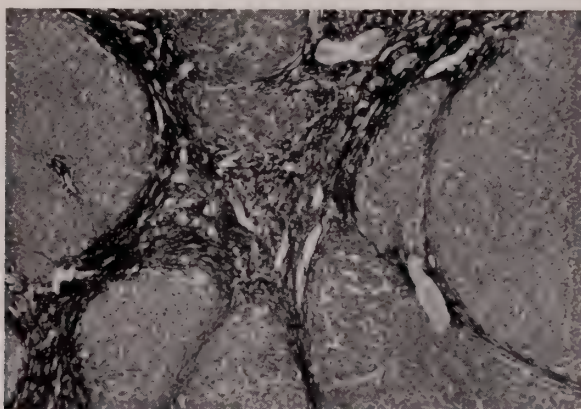


FIG. 1. Microscopic section of liver showing large irregular nodules. (CAB $\times 63$)

The liver weighed 3,370 grams. The entire liver was nodular, the nodules varying in size and color. Microscopically, some areas contained small nodules completely devoid of architecture as seen in Laennec's cirrhosis. Other areas contained predominantly large irregular nodules within which fine central veins and small portal tracts could be identified, giving the picture of postnecrotic cirrhosis (Fig. 1). This picture is thought to develop from the continued expansion of the small nodules of Laennec's cirrhosis, which become restructured in the sense that new central veins and portal tracts develop within them. This mixed picture therefore is considered to be a late stage of alcoholic cirrhosis.

The spleen was enlarged, weighing 540 grams and showing extensive congestion. Small gastric and esophageal varices were found microscopically. The pancreatic islets were morphologically normal, as they often are in diabetes. An incidental finding was a small lipoma of the adrenal.

The kidneys were also enlarged, the left weighing 450 grams, the right 210 grams. The right kidney had an unusual appearance (Fig. 2). The upper third was shrunken and smooth, while the lower two-thirds appeared enlarged and

was quite granular. On section a well-defined corticomedullary junction could be seen in the lower portion of the kidney, but not in the upper portion. The kidney was found to have a single pelvis and ureter; however, there were two separate renal arteries with separate points of origin in the ureter. Both renal arteries showed severe arteriosclerosis, the upper one being almost entirely occluded except for a pinpoint lumen (Fig. 3). The shrunken upper portion of the kidney which received its blood supply through the almost entirely occluded vessel showed almost complete atrophy with disappearance of the renal tubules but preservation of the glomeruli which were bunched closely together. The tubules

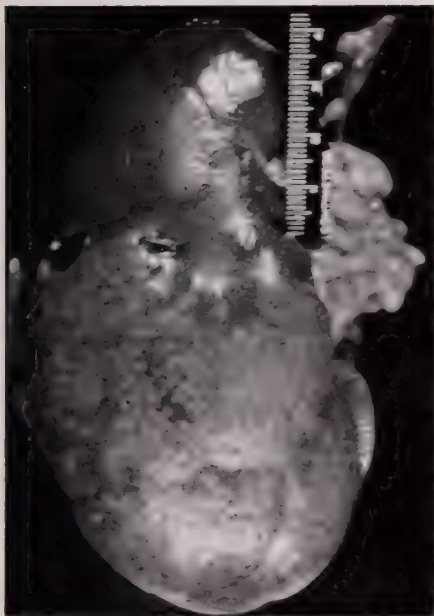


FIG. 2.

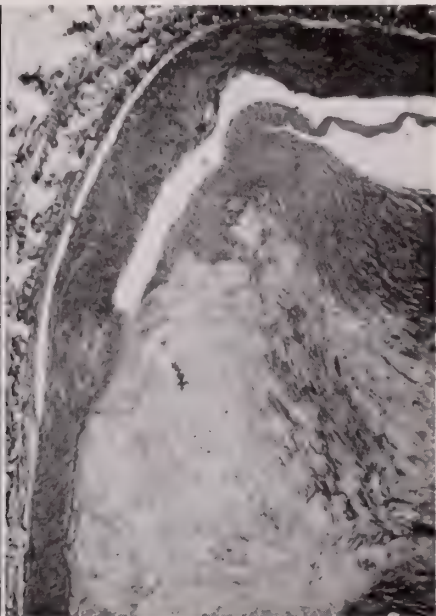


FIG. 3.

FIG. 2. Gross picture of right kidney with atrophic upper third.
FIG. 3. Small lumen in occluded right upper renal artery. (CAB $\times 63$)

which remained in this area were exceedingly small and were surrounded by large amounts of connective tissue (Fig. 4). The arterioles in the affected portion did not show any marked changes.

In the remainder of the right kidney and in the left kidney there was extensive arteriolar nephrosclerosis. PAS stain of these areas revealed PAS positive thickening of the intercapillary spaces as seen in diffuse intercapillary glomerulosclerosis (Fig. 5).

Tubular atrophy as the main change of gradually progressive renal ischemia is a well-known phenomenon. While it is usually associated with hypertension, in this particular case we cannot blame the renal atrophy alone for the hypertension because we do not know the temporal sequence of events. It is almost certain,

however, that these renal changes at least contributed to the patient's hypertensive state.

Intercapillary glomerulosclerosis, which appears to consist primarily of a deposition of basement membranelike material in the intercapillary spaces, has been found in all cases of diabetes that have so far been studied by electron microscopy, even before there were clinical symptoms of diabetes or of nephropathy. Since the material deposited has many of the morphological characteristics of basement membrane, it is readily demonstrated by the PAS stain.

I think in essence we have been able to confirm Dr. Ellenberg's diagnoses.

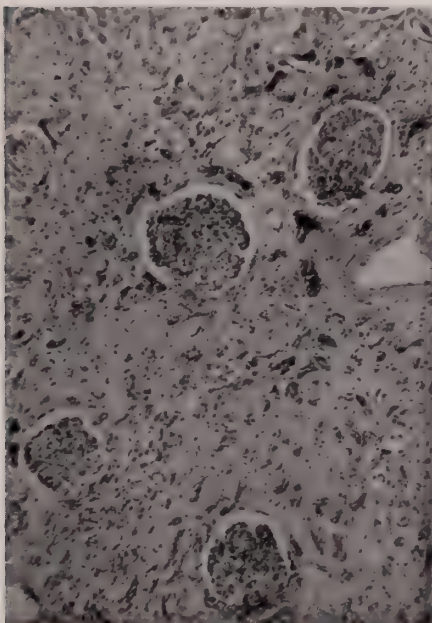


FIG. 4.

FIG. 4. Tubular atrophy in upper portion of left kidney. (H & E $\times 120$)

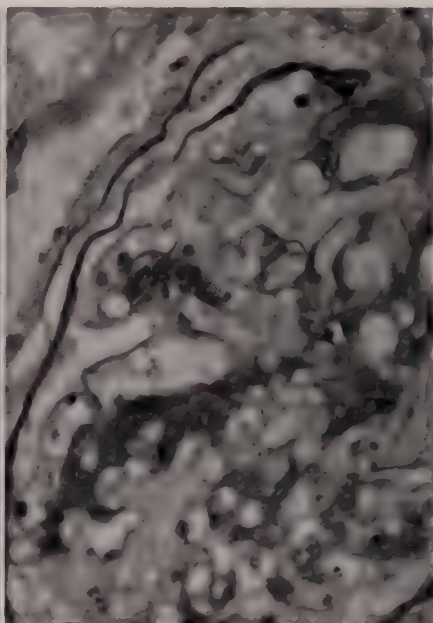


FIG. 5.

FIG. 5. Intercapillary glomerulosclerosis with thick deposition of polysaccharide material in intercapillary spaces. (PAS $\times 560$)

There was no evidence clinically of the partial occlusion of the right upper renal artery.

Dr. Ellenberg: I should have pointed out that there must be something in addition to the renal glomerular involvement to explain some of the hypertension because when hypertension in a diabetic is limited to an expression of the renal glomerular involvement, it is usually of a rather mild degree. We do not see blood pressures like 210/140 unless there are some other factors involved, such as essential hypertension. This would fit in with the obstructed right renal vessel.

I was hoping you could explain the recurrent pneumonias because this is the one thing that really bothered me. Diabetics have so many complications that

when one tries to fit the complications into the picture of diabetes, one is usually correct. Finally, to repeat, the incidence and severity of complications are not at all necessarily related, as in this particular instance, to the severity of diabetes as measured by carbohydrate metabolic disorder.

Final diagnoses:

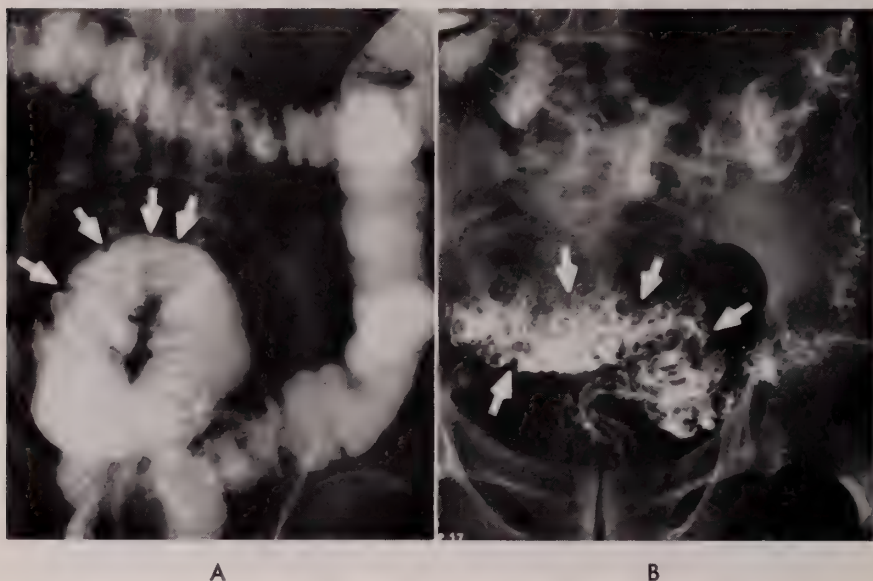
1. MYOCARDIAL INFARCTION, POSTERIOR WALL OF LEFT VENTRICLE, SEVERAL DAYS OLD, WITH PASSIVE CONGESTION OF LUNGS, SPLEEN AND KIDNEYS. 2. ARTERIOSCLEROTIC OCCLUSION OF RIGHT UPPER RENAL ARTERY WITH ISCHEMIC ATROPHY OF UPPER PORTION OF RIGHT KIDNEY. 3. SEPTAL CIRRHOSIS WITH POSTNECROTIC FEATURES. 4. ADRENAL LIPOMA. 5. DIABETIC INTERCAPILLARY GLOMERULOSCLEROSIS, DIFFUSE TYPE. 6. DIABETES MELLITUS (CLINICAL).

Radiological Notes

CLAUDE BLOCH, M.D. AND HARVEY M. PECK, M.D., *Co-Editors*
New York, N. Y.

CASE NO. 173

A 72 year old male was admitted to the hospital for evaluation of a hearing deficit. During the preceding five years, he had noted a 35 pound weight



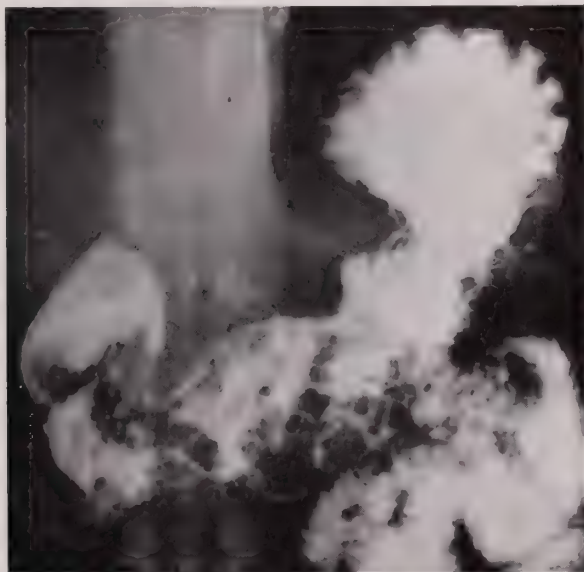
Case 173, Fig. 1A. Barium enema reveals numerous small nodular defects in the sigmoid, most marked along the superior contour (arrows). The lumen of the bowel is normal. No ulcerations are seen. Similar mucosal alterations are noted within the transverse colon.

Case 173, Fig. 1B. Postevacuation film demonstrates the marked thickening and extensive distortion of the mucosal folds in the sigmoid colon (arrows).

loss, increasing weakness, tiredness and occasional dizziness. There was no melena or hematemesis. Physical examination revealed a chronically ill, pale man in no distress. There was no evidence of peripheral adenopathy. Abdominal examination revealed a normal liver and spleen. There were no palpable masses. Laboratory examination revealed a severe hypochronic anemia. Stool guaiac examinations were persistently positive.

Because of these findings, a barium enema was performed as the first part of the investigation of the intestinal tract. This revealed numerous small nodu-

lar defects along the contours of the sigmoid (Fig. 1A) associated with marked thickening and distortion of the mucosal folds (Fig. 1B). The caliber of the bowel was normal and no discrete filling defects or ulcerations were demonstrated. Similar but somewhat less pronounced changes were noted within the transverse colon. A diagnosis of diffuse lymphoma was suggested and barium meal was requested. Within the stomach, the rugal folds were diffusely thickened and distorted by numerous small nodular infiltrations (Fig. 2A). The walls were relatively nondistensible with impaired peristalsis along both curvatures. No localized areas of narrowing and no discrete ulcerations were noted within the stomach. Numerous tiny spiculations were present along the lesser



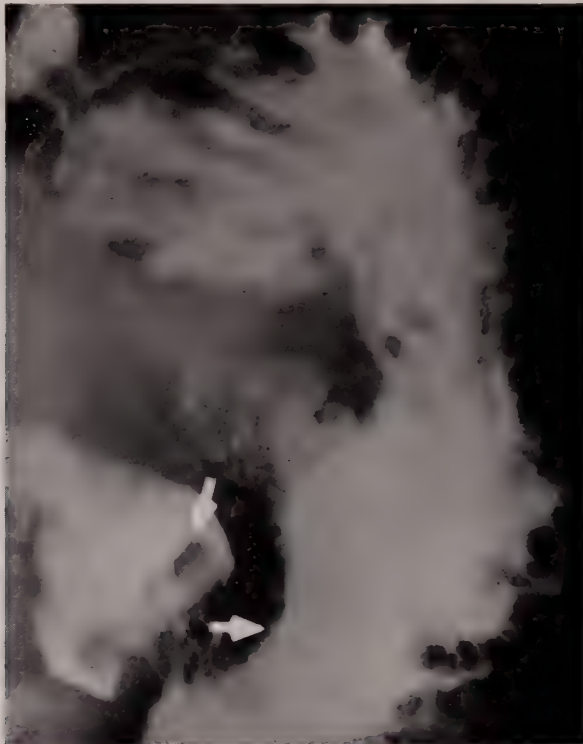
Case 173, Fig. 2A. Barium meal examination reveals marked thickening and distortion of the rugal folds by diffuse nodular infiltrations. No localized areas of narrowing and no discrete ulcerations are noted within the stomach.

curvature, predominantly in the antral region. The duodenal bulb was large but not deformed. Numerous irregular nodular defects were present in the duodenal bulb, especially at the base (Fig. 2B). Similar but less prominent changes were noted within the descending duodenum. The jejunum and ileum were normal.

Endoscopic biopsies of the sigmoid and stomach were then performed. The mucosa of both regions was found to be diffusely infiltrated by large mature lymphocytes. There was no evidence of involvement of the deeper layers of the bowel wall. The pathological report was "benign lymphoma." Bone marrow aspiration revealed no abnormal cells and the peripheral blood count showed a mild leukocytosis with a slight shift to the left. Blood electrolytes and serum electrophoresis were normal. The patient was given a course of x-ray therapy to the entire abdomen with prompt relief of symptoms.

DISCUSSION

The entity of "benign lymphoma" of the gastrointestinal tract has also been referred to in the literature as "pseudoleukemia intestinalis" (1, 2, 5), and represents a small proportion of many of the large series of cases reviewed in the literature on lymphoid tumors of the gastrointestinal tract (3, 6). There is considerable confusion in the literature both clinically and pathologically in regard to the benign lymphoid hyperplasias and "benign lymphomas" of the



Case 173, Fig. 2B. Numerous spiculations are seen along the lesser curvature of the stomach, most prominent within the antrum (lower arrow). The duodenal bulb is large but not deformed. Numerous irregular nodular defects are present within the duodenal bulb especially at its base (upper arrow).

gastrointestinal tract. The prognosis of benign lymphoma appears to be generally good and is not influenced by whether a single portion of the gastrointestinal tract or the entire intestinal tract is involved. Pathologically, there is a hyperplasia of the lymphoid elements within the mucosa and submucosa without any gross or histological evidence of deep infiltration or destruction of the normal architecture of the intestinal wall such as is found in the lymphosarcomas and other malignant lymphomas (5). Grossly, the mucosa is widely altered with cobblestoning or discrete polypoid formation. At laparotomy, the

soft polypoid mucosal and submucosal lesions are difficult to palpate and the extent of the disease is best judged by x-ray examination of the alimentary tract. Although skip lesions occasionally occur, the entire gastrointestinal tract is usually affected, especially when there is evidence of disease of both the stomach and colon. As in the case presented, there is often no evidence of peripheral glandular enlargement or hepatosplenomegaly. Roentgenologically, the findings are those of a diffuse mucosal alteration with no evidence of discrete ulceration or significant narrowing of the lumen of the bowel. There is usually no evidence of mesenteric or retroperitoneal lymph node enlargement. In most cases, it is impossible to differentiate this disease from the ordinary type of gastrointestinal lymphosarcoma by x-ray examination alone.

The entity of benign lymphoma of the rectum and anal canal is treated as a separate entity in the literature. This is probably due to the universally good prognosis for this disease and to the fact that it never becomes a generalized process. In this disease, there is usually a sessile or pedunculated rectal polypoid mass which ulcerates and bleeds easily. Pathologically, the findings are the same as in benign lymphoma of the gastrointestinal tract with mucosal and submucosal follicular hyperplasia and no evidence of infiltration of the deep layers.

The treatment for benign lymphoma of the gastrointestinal tract is radiation therapy to the entire abdomen. It is usually possible to demonstrate complete disappearance of the mucosal and submucosal infiltrations.

Case Report: "BENIGN LYMPHOMA" OF THE STOMACH, DUODENUM AND COLON.

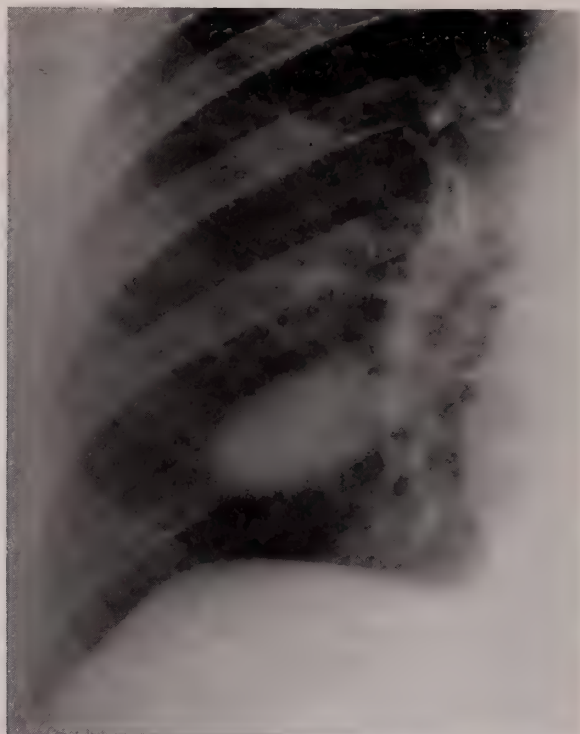
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CASE NO. 174

A 66 year old female was admitted to the hospital because of a lesion in the right lower lung field. Four months prior to admission, the patient had a productive cough associated with pain in the left chest. After symptomatic therapy, cough and sputum disappeared but pain persisted. Three months prior to admission, the pain shifted to the right chest posteriorly. Roentgen examination of the chest at this time revealed a mass in the right lower lobe. Past history included two bouts of pneumonia, 35 and 10 years prior to admission, the latter associated with a left pleural effusion requiring two thoracenteses. A chest film performed 1½ years prior to admission and reviewed at this time was

normal. Physical examination revealed slight tenderness over the left anterior ribs. There were no abnormal signs in the chest. There was no evidence of clubbing or lymphadenopathy. The liver and spleen were not felt. Routine laboratory examinations were negative except for a markedly positive first strength PPD. Bronchial washings were negative for tumor cells. A right scalene fat pad biopsy was normal. Bronchoscopy revealed a small amount of blood at the orifice of the superior segment of the right lower lobe. Biopsy of this area

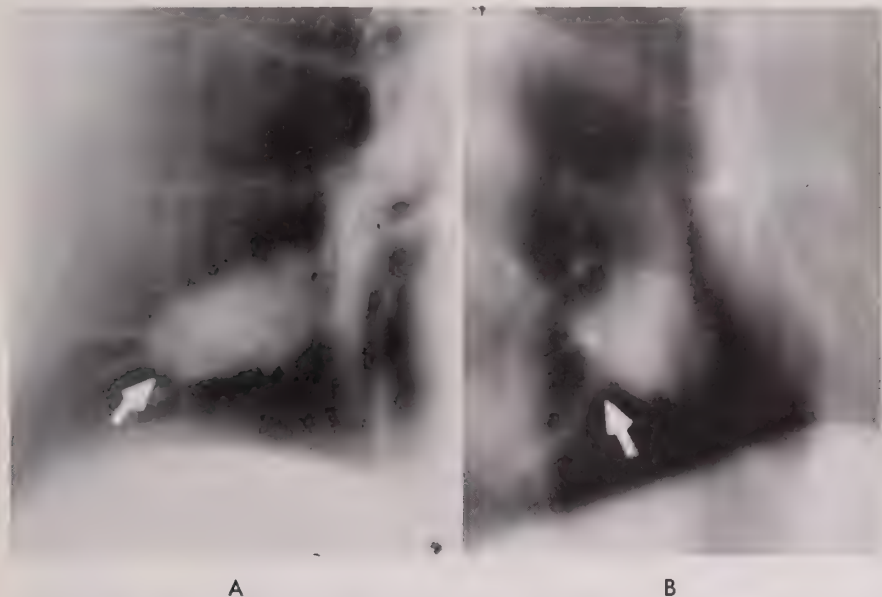


Case 174, Fig. 1. Postero-anterior examination of the chest reveals a 4×2 cm ovoid homogeneous density in the right lower lobe which is well margined but slightly fuzzy in outline. The heart and lungs are otherwise normal.

showed chronic bronchitis. The patient was placed on antituberculous therapy. Repeat chest film after a five week interval revealed a 4×2 cm ovoid homogeneous density in the right lower lobe which was well margined but slightly fuzzy in outline (Fig. 1). This lesion was increased in size minimally in comparison with the previous examination. Tomography (Figs. 2A and 2B) revealed no calcifications or cavities.

Thoracotomy was performed which revealed an almond-sized mass measuring $2 \times 3 \times 5$ cm in the anterior basal segment of the right lower lobe near the hilum. The overlying pleura appeared normal. There was no evidence of any abnormality of the hilar nodes. A right lower lobectomy was performed and

the mediastinal nodes were biopsied. The pathological report was that of a solitary, oval, nonencapsulated nodule of small cell lymphosarcoma. The segmental bronchus which traversed the mass was distorted but not obstructed. The mediastinal and subcarinal nodes were normal. The patient made an uneventful recovery.



Case 174, Fig. 2A. Postero-anterior tomogram through the center of the lesion reveals a sharply outlined inferolateral contour (arrow), and a fuzzy superomedial border.

Case 174, Fig. 2B. Lateral tomogram reveals a linear density projecting from the postero-inferior contour of the lesion which has the appearance of a blood vessel. While this feature suggests the possibility of an arteriovenous anomaly, the vessel is not dilated or tortuous and extends peripherally rather than centrally towards the hilum. No calcifications or cavities are noted.

DISCUSSION

Primary lymphosarcoma of the lung is a rare disease with fewer than fifty documented cases in the English and American literature (1, 2, 4, 5). In contradistinction, up to one-third of patients with generalized malignant lymphoma have some involvement of the lungs or pleura pathologically (2) and an estimated 5 per cent to 10 per cent have radiographic findings (6). In 814 cases of malignant lymphomas involving the lungs, only a single case of primary pulmonary lymphosarcoma was found (3, 7).

There is no typical clinical symptomatology. Diagnosis is rarely made prior to thoracotomy. Pathologically, the lesion usually is infiltrating or replacing lung parenchyma. When small it may be circumscribed, but is never truly encapsulated.

sulated. It may involve an entire lobe or lobes and can cross fissures. Bronchial mucosal involvement seldom occurs, but bronchi are often compressed or distorted. The histologic picture in most instances is that of small cell lymphosarcoma.

Radiographic appearance is not distinctive. When small, the lesion may be well circumscribed and fairly sharp in outline as illustrated by the case described. These features should not be confused with the exquisitely sharp margins of a radiographically benign lesion. Usually the lesion is more extensive when first discovered and the appearance then simulates that of a carcinoma, or in some instances, chronic pneumonia. One differential diagnostic feature has been pointed out by Baron and Whitehouse (1). With bronchography, they demonstrated patent bronchi traversing the lesion in some of their cases. Distortion and displacement of bronchi did occur, but bronchial obstruction was not observed. This feature correlates well with the gross pathological findings.

Case Report: PRIMARY LYMPHOSARCOMA OF THE LUNG.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Paul Kirschner.

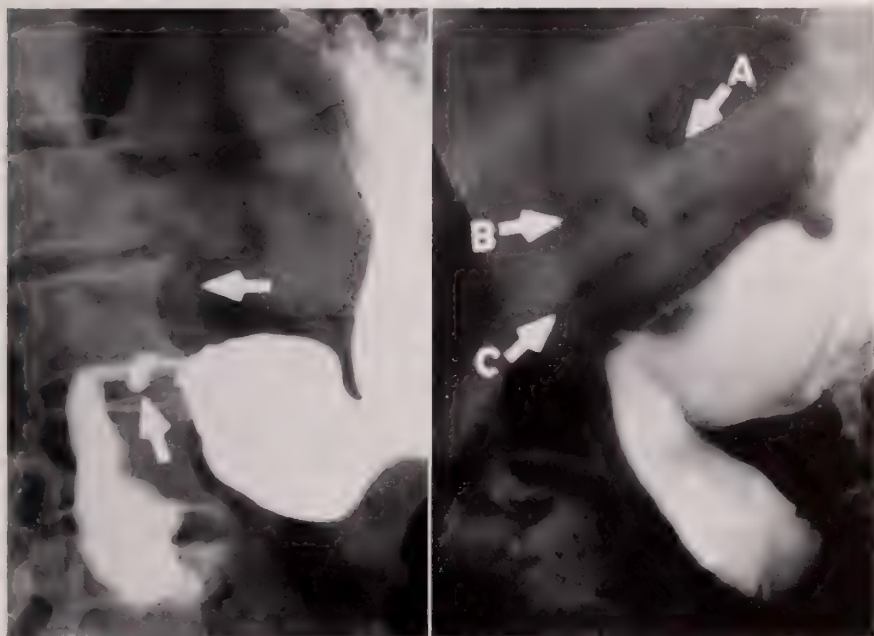
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CASE NO. 175

A 64 year old female was admitted to the hospital because of severe vomiting and epigastric pain. Symptoms began abruptly ten days before admission when, after consuming a large meal, the patient experienced severe epigastric pain, nausea and vomiting. Intermittent symptoms persisted for a few days and were exacerbated on the day of admission. The patient had a known duodenal ulcer for 24 years with four episodes of hematemesis and melena. In the months prior to the present illness, long-standing symptoms of epigastric pain were increased and the duodenal ulcer was thought to be active. A gastrointestinal

series was performed two months prior to admission. The duodenal bulb was markedly deformed in a clover-leaf fashion and a small ulcer crater was thought to be present (Fig. 1A). The stomach emptied well. A 5 x 3 cm, faintly calcified gall stone was noted superior to the duodenal bulb. There was gas in the common duct and gall bladder (Fig. 1B).



A

B

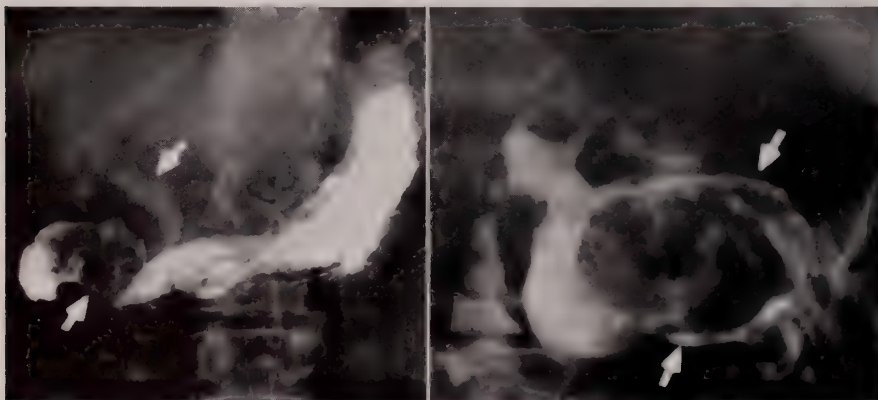
Case 175, Fig. 1A. Prone right anterior oblique film demonstrates a marked clover-leaf deformity of the duodenal bulb (lower arrow). A tiny patch of barium in the midportion of the bulb represents an ulcer crater. The stomach is normal in size. A faint ring calcification is noted above the duodenal bulb (upper arrow).

Case 175, Fig. 1B. Prone postero-anterior film demonstrates gas within the common bile duct (arrow A) and the gall bladder (arrow B). A 5 x 3 cm faintly calcified gall stone is noted superior to the duodenal bulb (arrow C).

Repeat gastrointestinal series on admission revealed a totally obstructed, markedly dilated stomach which contained large amounts of fluid (Fig. 2). The pyloric region was never well outlined with barium. The gall stone and air in the biliary tract were noted. At laparotomy, a large biliary calculus measuring 4 x 2.5 cm was found lodged inside the duodenal bulb. The gall bladder was fused to the duodenal bulb at the site of cholecystoduodenal fistula. The stone was milked into the stomach and removed by gastrotomy. No additional procedure was performed. The patient made an uneventful recovery.



Case 175, Fig. 2. Upright postero-anterior film demonstrates a broad fluid level in the stomach. An air-fluid level is seen in the distal antrum (lower arrow). The calcified gall stone is again noted.



A

B

Case 175, Fig. 3A. Another case of cholecystoduodenal fistula with barium in the common bile duct (upper arrow). There is a large ill-defined filling defect within the duodenal bulb (lower arrow).

Case 175, Fig. 3B. Spot film of the duodenal bulb reveals the filling defect to be well circumscribed (between arrows). This represents a gall stone. (This case is presented through the courtesy of Dr. A. Z. Freudenheim, Good Samaritan Hospital, Suffern, N. Y.)

Case Report: CHOLECYSTODUODENAL FISTULA WITH GALL STONE OBSTRUCTION OF THE DUODENAL BULB ASSOCIATED WITH DUODENAL ULCER.

(SEE DISCUSSION IN CASE NO. 176)

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Samuel Gelband and Dr. James J. Finnerty, Patchogue, N. Y.

CASE NO. 176

A 72 year old female was admitted to the hospital with the chief complaint of lower abdominal pain. The present illness was of three weeks' duration and started abruptly with upper abdominal pain, nausea and vomiting. This was followed by lower abdominal cramps, distention and frequent loose scanty bowel movements. A hysterectomy was performed 22 years prior to admission. The patient denied significant digestive difficulties, colic and jaundice. On physical examination, the temperature and pulse were moderately elevated. There were signs of moderate dehydration, abdominal distention and diffuse abdominal tenderness, most marked in the left lower quadrant. The diagnosis of partial left sided colonic obstruction was entertained.

Radiological examination of the abdomen (Fig. 1) revealed a gas-filled biliary tree with the common duct measuring 1.5 cm in diameter. A pear-shaped gas shadow in the right upper quadrant located above the colon and lateral to the common duct was interpreted as a gas-filled gall bladder. The colon was moderately dilated with fluid and some gas. No gas or stool was identified in the rectum and sigmoid. An opaque calculus was not seen. The diagnosis of cholecystocolic fistula with gall stone obstruction of the sigmoid was suggested. Barium enema (Figs. 2 and 3) revealed a large smooth intraluminal filling defect in the sigmoid which produced almost complete retrograde obstruction. This was interpreted as a gall stone. The segment of the bowel just distal to it was narrowed but a definite constricting neoplasm could not be demonstrated. The site of fistulous communication was not outlined.

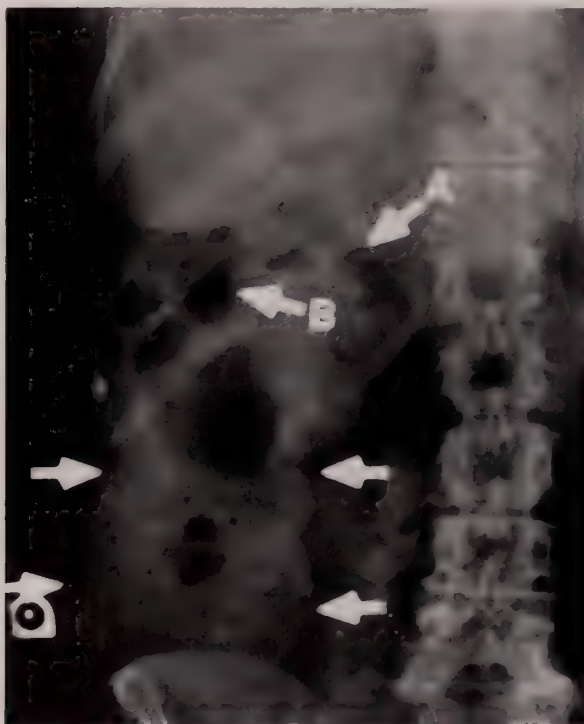
Sigmoidoscopic examination revealed an obstruction of 12 cm, where edematous mucosa was observed. There was no indication of neoplasm.

Gastrointestinal series, using water soluble opaque material, showed a normal stomach and duodenal bulb. The second portion of the duodenum was irritable. The gall bladder was not opacified on the early films. A late film demonstrated a narrowed segment in the hepatic flexure intimately associated with an opacified gall bladder, apparently the site of fistulization.

The patient was treated conservatively. On the seventh hospital day, a 5 cm ovoid gall stone was spontaneously passed per rectum. This was followed by rapid clinical improvement. Repeat barium enema examination clearly demonstrated the cholecystocolic fistula (Fig. 4). The remainder of the colon was normal. Another study performed six months later when the patient was asymptomatic showed no change.

DISCUSSION

Gall stone obstructions usually occur at the sites of normal anatomic narrowing or narrowing related to local pathologic processes. They may be divided into three categories: small bowel, large bowel and gastroduodenal. Such cases comprise about two per cent of mechanical obstructions in the adult (2, 3, 8).



Case 176, Fig. 1. Prone film of the abdomen reveals gas in the common duct and hepatic radicles (arrow A). There is a pear-shaped gas shadow above the hepatic flexure interpreted as the gall bladder (arrow B). The right colon is moderately dilated (between arrows) and the left colon slightly dilated, both filled with liquid contents. No stool or gas is seen in the rectum and sigmoid. An opaque calculus is not identified.

Small bowel obstruction accounts for about ninety per cent of cases, and the stone is usually lodged one or two feet proximal to the ileocecal valve, a zone of minimum small bowel diameter. Cholecystoduodenal fistula is usually present. Such cases of "gall stone ileus" are common and account for 25 per cent of mechanical small bowel obstructions in patients over 70 years of age (3). Large bowel and gastroduodenal obstructions, as illustrated by the cases reported, are the more unusual types of obstruction.

In large bowel obstruction, the stone usually enters the colon via cholecystocolic fistula at the hepatic flexure, although a stone can enter at the duodenal level and traverse the entire small bowel successfully before obstructing the

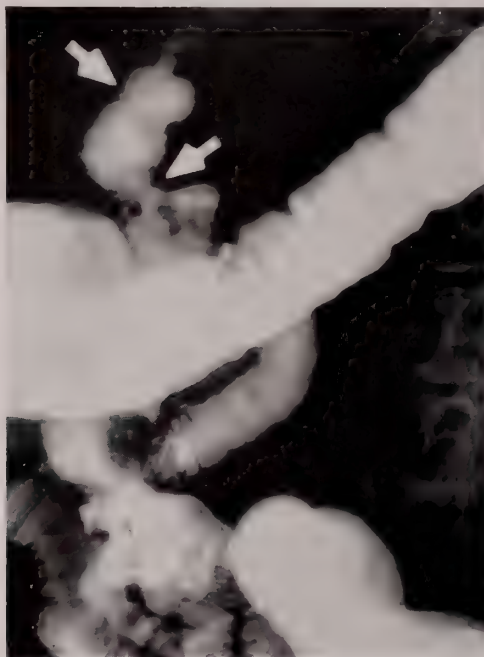


Case 176, Fig. 2. Spot film of the sigmoid demonstrates a large, smooth obstructing intraluminal mass (arrow). A thickened transverse fold is noted just distal to the mass where the bowel lumen is narrowed. The contours here are smooth.



Case 176, Fig. 3. Prone postevacuation film demonstrates complete emptying of the rectum but retention of diluted barium proximal to the obstructing sigmoid mass (arrow). Gas in the common duct is again noted.

colon (4). The site of colonic obstruction is almost invariably in the sigmoid, where the minimum diameter of about 2.5 cm is found. (A single case of obstruction in the transverse colon is reported (10).) Furthermore, the sigmoid is a frequent site of inflammatory or neoplastic narrowing, particularly in older people. Another reason for sigmoid localization may be the relative lack of forward propulsive movements and a tendency for strong contractions of circular muscle and spasm to occur in this segment (9). When colonic obstruction has been established, spontaneous relief with passage of the stone, as occurred in the case presented, is not common (7).



Case 176, Fig. 4. The gallbladder is filled via cholecystocolic fistula.

In gastroduodenal obstruction, the stone may enter either the duodenum or the gastric antrum. Actual fistulization need not occur and obstruction can be produced with the stone in a submucous location (1). The presence of a chronic duodenal ulcer as seen in the case presented has significance both as a cause for fistulization as well as a site of obstruction. As in cases with colonic obstruction, however, relief of obstruction following emesis of the calculus has been reported (6).

Radiologic recognition of gall stone obstruction is based upon the criteria described by Rigler *et al.* (5):

- a) Recognition of the air (or barium) cholangiogram. This is presumptive evidence of internal biliary fistula.
- b) Visualization of the stone in the gastrointestinal tract, either on plain films or on contrast study.

c) Demonstration of a significant change in position of a gall stone. The knowledge of the former presence of a biliary calculus which is no longer seen in the right upper quadrant satisfies this criterion.

d) Evidence of obstruction of the gastrointestinal tract.

Differential diagnosis of the stone *in situ* includes foreign body and polypoid neoplasm. In the sigmoid, coprolith and fecal impaction are to be considered. In the stomach and duodenum, particularly with the submucous location of the stone, malignant infiltrations, submucosal tumors, and extrinsic defects (both inflammatory and neoplastic) should be included.

Case Report: CHOLECYSTOCOLIC FISTULA WITH GALL STONE OBSTRUCTION OF THE SIGMOID.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Paul S. Ingrassia and A. Z. Freudenheim, Good Samaritan Hospital, Suffern, N. Y.

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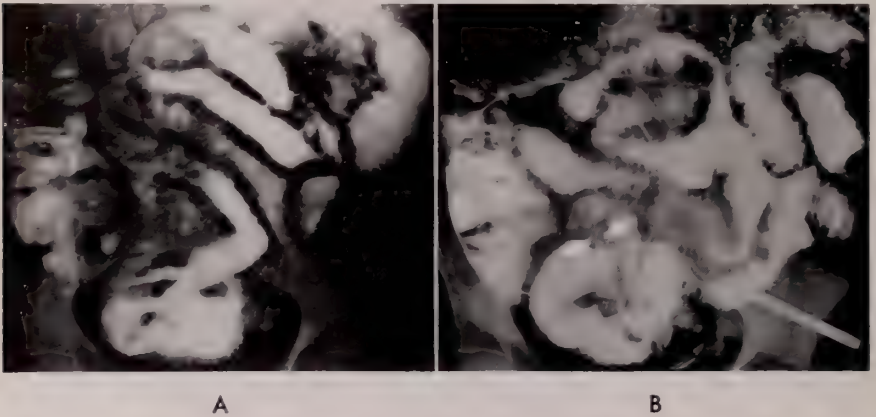
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CASE NO. 177

A 38 year old male was admitted to the hospital with a thirty pound weight loss during the preceding six months. Four years before, the patient noted progressive swelling of the left testicle. An orchiectomy was performed. Pathological examination revealed a seminoma. He was given radiotherapy to the left groin, pelvis and para-aortic areas. The exact dosage or details of therapy are not available, but presumably a midplane dosage of 3,500 r in five weeks was administered. The patient remained well until six months before admission when he had severe right lower quadrant pain. An exploratory laparotomy was performed at that time and the ileum was found to be congested and edematous. No resection was performed, but the impression was that the bowel was in-

volved with regional enteritis. After operation, the patient continued to have crampy lower abdominal pains of a persistent and progressive nature accompanied by weight loss. No diarrhea, melena or vomiting was noted. The patient was pale, thin and chronically ill. No masses or point tenderness were noted in the abdomen. There was no clinical evidence of ascites. No radiation skin changes were noted over the abdomen or back. Laboratory examination revealed a normal hemogram and normal blood proteins and electrolytes.

Barium meal examination revealed no abnormalities of the esophagus, stomach or duodenum. The jejunum and proximal ileum were moderately dilated and contained increased secretions. The valvulae conniventes were considera-



Case 177, Fig. 1A. Small bowel examination reveals moderate dilatation and increased secretions in the jejunum and proximal ileum. The mucosal folds are diffusely thickened and nonpliable. The loops are separated. Multiple areas of narrowing in the proximal small bowel are transient in nature.

Case 177, Fig. 1B. Later film reveals a persistent narrowing in the distal ileum (between arrows) with proximal dilatation. The mucosal folds are again noted to be diffusely thickened and distorted.

bly thickened but remained pliable. There were a moderate number of transient areas of narrowing within the proximal ileum causing no delay to the passage of barium. The entire distal ileum was the seat of a diffuse inflammatory process characterized by thickening and rigidity of the valvulae conniventes, serrated borders with tiny spiculations, and moderate separation of adjacent bowel loops. There was a short area of narrowing in the distal ileum within the pelvis, slightly to the right of the midline. The contours of the narrowed segment were slightly irregular but concentric. No gross filling defects or extrinsic mass were noted. Discrete ulcerations were not seen. Barium entered the colon slowly. The terminal ileum was best visualized by retrograde reflux during a barium enema and appeared normal. The colon was normal. The findings were interpreted as radiation enteritis with a strictured area in the distal ileum.

At laparotomy, a short segment of narrowing was identified in the distal ileum, approximately 30 cm from the ileocecal valve. The entire small bowel was lusterless and there were a few areas of telangiectasia. The strictured segment of bowel was thickened and firm. The mucosa was effaced but no discrete ulcerations were identified. Microscopically, the involved bowel revealed fibrosis and endarteritis consistent with radiation changes. An ileocolic resection was performed and the patient had an uneventful postoperative course with prompt disappearance of his symptoms.

DISCUSSION

Radiation enteritis is a rare complication of x-ray therapy directed to the abdomen. Most cases reported in the literature follow pelvic radiation combined with intracavitary radium used in the treatment of uterine carcinomas. In the usual case, a midplane dose of 5,000 r or more is necessary to cause radiation damage to the intestines. This usually occurs when a single loop of intestine is adherent in the pelvis and thus receives a full cancericidal dose. Usually, when the bowel is freely movable, any one loop of bowel is not subjected to the full dose of radiation. Radiation ileitis is a rare complication of radiotherapy given in seminomas of the testis, because the dose administered to the abdomen and retroperitoneal regions is usually well below the above described level. In the current case, it is conceivable that there was a significant overlap of the borders of the various fields, thereby exposing a small volume of tissue to twice the calculated dose.

There is usually a latent period of 5 to 16 months after the cessation of therapy before symptoms of radiation enteritis occur (6). Patients have signs of subacute intestinal obstruction and are usually chronically ill with weight loss, secondary anemias and hypoproteinemias. In a few cases entero-enteric or enterovesical fistulas have been described (1, 5). The gross pathological findings are those of loss of luster of the peritoneum which is thickened and within which areas of telangiectasia are noted. The affected bowel is thickened and shows loss of normal flexibility. In a few cases, there are local areas of necrosis of the bowel accompanied by local or generalized peritonitis (2, 3). Upon opening the bowel, the mucosa can be seen to be ulcerated. In the areas of ulceration, there is narrowing accompanied by fibrosis. Warren has described pathognomonic changes which are noted microscopically in the affected bowel (4). These include hyalinization of connective tissue, large abnormal fibroblasts, and blood vessels within the wall of the bowel showing hyaline degeneration. Also noted are atypical endothelial cells, phlebosclerosis and degeneration of the muscularis mucosa. Both roentgenologically and grossly the differential diagnosis is primarily with regional enteritis (Crohn's disease). In both conditions, the small bowel is thickened and ulcerated with secondary partial small bowel obstruction. The important difference is that in Crohn's disease the terminal ileum is almost always maximally involved, whereas in radiation enteritis any loop of intestine located in the pelvis can be the seat of the inflammatory process.

Case Report: RADIATION ILEITIS.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Henry D. Janowitz.

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CASE NO. 178

A 46 year old male was admitted to the hospital for thoracotomy. The patient had been perfectly well until two months prior to admission when a loose cough developed, productive of small amounts of mucoid sputum. There was no fever, hemoptysis or other physical complaint. Antibiotic therapy was not of dramatic help and symptoms gradually subsided. A chest film was made six weeks prior to admission during the course of the illness which revealed a mass in the right hilar region. Past history, occupational history, review of systems, physical examination, and routine studies of the blood and urine were non-contributory. The patient never had a previous roentgen examination of the chest.

On admission, repeat chest film (Fig. 1) revealed a rounded, sharply outlined mass in the right hilum. There was no change in comparison with the previous study. Frontal and lateral tomography (Figs. 2A and 2B) revealed no cavities or calcifications. The mass was located just below and behind the middle lobe bronchus at the root. The bronchi were not distorted or displaced.

Bronchoscopy was normal and bronchial smears and washings were negative for tumor cells. At thoracotomy, a 4 cm mass was located in the hilum at the major fissure between the middle and lower lobes. The mass was "shelled out" without technical difficulty.

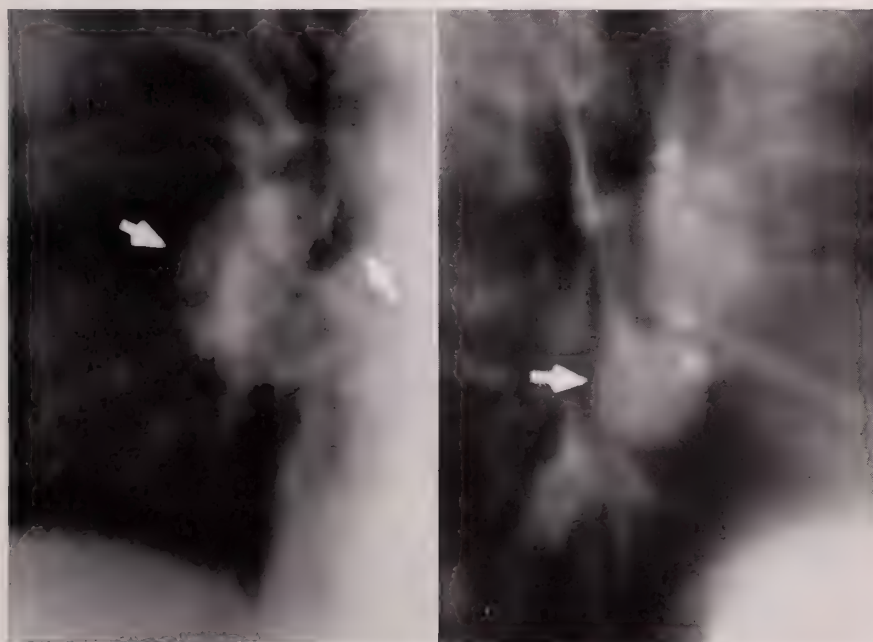
Pathological report (Dr. Robert T. Bryan) revealed an enlarged lymph node with normal architecture. There were small patches of fibrosis and hyalinization and an increased number of eosinophiles. There were no Reed-Sternberg cells or neoplastic cells. The final diagnosis was "reactive hyperplasia" in a hilar lymph node.

DISCUSSION

In 1954, Castleman described a case of a large anterior mediastinal mass thought to be a thymic tumor which proved histologically to be hyperplastic lymph nodes (1). In 1956, he and his colleagues collected 13 similar cases and established a new pathological entity (2). The process has occurred most often



Case 178, Fig. 1. Postero-anterior chest film reveals a rounded sharply outlined mass in the right hilum. The heart and lungs are otherwise normal.



A

B

Case 178, Fig. 2A. Frontal tomogram.

Case 178, Fig. 2B. Lateral tomogram. The mass is located just below and behind the middle lobe bronchus at the root. There are no cavities or calcifications. The bronchi are normal in course and caliber.

at the lung root or tracheobronchial region. A few cases have appeared in the anterior mediastinum. A report of a case (3) in the posterior mediastinum is also available.

The etiology is obscure. For the present, the disease is regarded as a response to inflammation (2). Reflecting this concept, the nomenclature has included "chronic lymphadenitis" and "lymph node hyperplasia;" the designation "Castleman's disease" also seems appropriate.

Radiographically, lesions at the root cannot be differentiated from malignant lymphoma, granulomatous lymph node enlargement, and primary and secondary neoplasm. In the anterior mediastinum, the picture is that of thymic tumor or malignant lymphoma. The lesion reported in the posterior mediastinum presented all the radiographic features of a neurofibroma. The diagnosis is made only following thoracotomy. The prognosis is excellent and no reports have appeared of recurrence or metastases.

Case Report: LOCALIZED BENIGN LYMPH NODE HYPERPLASIA, RIGHT HILUM (CASTLEMAN'S DISEASE).

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Sheldon B. Adler and A. Z. Freudenheim, Good Samaritan Hospital Suffern, N. Y.

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Abstracts

Papers Presented before the Research Club of The Mount Sinai Hospital

New York, N. Y.

The Relationship of Food and Water Intake in Aurothioglucose Obesity. Gerald Friedman, M.D., Ph.D., Jerome D. Waye, M.D., and Henry D. Janowitz, M.D.

Following LD₅₀ doses of ATG extensive damage to hypothalamic structures other than those strictly involved with food intake has been demonstrated. The injury to areas previously shown to be involved with the regulation of water intake prompted an investigation of the patterns of food and water intake in mice from the second day following ATG injection and daily thereafter for a period of six months. During the first week after ATG no statistically significant differences were noted as regards food and water intake and water to food ratios among mice destined to become obese, ATG nonobese mice or controls. From the second to the sixth months statistically significant increases in food and water intake were demonstrated among mice destined to become obese compared to ATG nonobese and control mice. Weight increments per animal over the six month period averaged 31.2 Gm for obese mice, 15.3 Gm for ATG nonobese mice and 11.3 Gm for controls. At no time period following the injection of ATG was there a demonstrable difference in water to food ratio among the three groups. It is concluded that alteration of water intake regulatory mechanisms following ATG is not a concomitant of aurothioglucose obesity.

Extracorporeal Circulation in Pulmonary Insufficiency. Isidore Kreel, M.D., and Howard Rappaport, M.D.

Acute, reversible hypoxia of pulmonary origin was induced in anesthetized experimental animals by forced ventilation of a gas of low oxygen content (i.e. 12% O₂, 2% CO₂, 86% N₂). When significant degrees of hypoxia were obtained, the animals were subjected to venovenous perfusion and oxygenation. Blood was drained from the inferior vena cava, oxygenated by a Kay-Cross rotating disc oxygenator, and pumped into the superior vena cava by a Sigma-motor pump.

In a series of animals subjected to this technique, hypoxia was effectively reversed for periods up to seven hours, with a high percentage of survival. However, when the duration of induced hypoxia and perfusion was prolonged beyond this (i.e. 8 to 20 hours) all animals died postperfusion, even though their hypoxia was effectively reversed during the operative period. In an effort to elucidate the cause of death, in this latter group, animals were perfused for prolonged periods (12-20 hours) without inducing hypoxia. All these animals survived, suggesting that the perfusion itself was not the limiting factor.

Studies are currently in progress to delineate the biochemical and hematologic changes during induced hypoxia and venovenous perfusion.

Preliminary Observations in Experimental, Isolated Left Heart Failure in Dogs. Richard P. Lasser, M.D., Isadore Kreel, M.D., Henry F. Mizgala, M.D., Stephen E. Furst, M.D., George Gabor, M.D., Douglas Allen, M.D., and Charles K. Friedberg, M.D.

The object of this study has been production of chronic, progressive, isolated left ventricular failure and study of the hemodynamic alterations and their relationship to renal function and sodium and water excretion.

To our knowledge such studies have not been reported, as previous work of this type has been confined to isolated right heart failure.

To produce controlled, isolated, left ventricular overload stress, a left subclavian artery-left atrial anastomosis was performed. This procedure was adopted after trials of left coronary artery embolization, several types of mitral insufficiency, and a left ventricular-left atrial shunt proved unsatisfactory.

The advantages of the subclavian artery-left atrial anastomosis are that it can be precisely regulated and quantitated, can be made to be variable, is surgically feasible, and can be occluded or taken down for studies in recovery.

Acute studies were made during operation of the aortic, right heart and left atrial pressure just prior to and immediately following opening of the shunt in twenty mongrel dogs.

Chronic studies were performed in four animals including selective aortic angiograms, left and right heart catheterization and renal function studies at monthly intervals in the awake animal as well as the response to rapid intravenous infusion of one liter of isotonic sodium chloride.

Results following the acute opening of the anastomosis revealed: 1) An immediate rise in left atrial pressure from an average of 2.9 mmHg to 5.1 mmHg; 2) Widening of the aortic pulse pressure from an average of 35 mmHg to 47 mmHg; 3) No significant change in mean aortic pressure or in heart rate.

Studies in four chronic survivors may be summarized as follows:

1. Angiograms: Shunts have remained patent for six months;
2. Hemodynamic measurements have shown progressive rise in left ventricular end diastolic pressure in three of the four animals from normal levels to 23, 30, and 10 mmHg respectively. "Reactive" pulmonary hypertension has been observed in two animals;
3. Renal responses to rapid saline loading have shown no tendency to sodium retention thus far in spite of elevation of left ventricular end diastolic pressure.

The Effects of Intrarenal Arterial Injection of Digitalis Glycosides on Urinary Concentration. Sherman Kupfer, M.D., and Jonah D. Kosovsky, M.D.

Maximally hydropenic dogs were prepared so that the functions of each kidney could be measured separately. In ten experiments, solute excretion was promoted by constant intravenous infusion of isotonic saline or 5% mannitol until the initial Cosm from each kidney was 1.35–4.02 cc min. Digoxin or strophanthin kombé was then injected (.05 mg/kg in 30 minutes) into one renal artery. The resultant ipsilateral diuresis was characterized by progressive increases in Cosm to peak values of 4.6–11.3 cc min whereas T³H₂O declined

steadily to 50–80% of that noted during the control periods. Seventy to 90 minutes after completion of the glycoside injection, a hypertonic solution of mannitol, urea, or sodium chloride was infused systemically to raise the rate of solute excretion in both kidneys. No increase in T^cH_2O occurred in the glycoside treated kidney. However, T^cH_2O in the control kidney rose gradually, as the availability of sodium for reabsorption in the ascending limb increased, until a peak value or plateau was reached at C_{osm} levels comparable to those observed in the experimental kidney after the glycoside injection. Digitalis glycosides thus depress T^cH_2O by a direct renal effect best interpreted, in the absence of changes in ADH responsiveness or intrarenal hemodynamics, as inhibition of sodium transport in the ascending limb.



“Treatment results were good, and in many cases a dramatic response was noted. Many of the cases had previously failed to respond to various types of therapy including, in some instances, other topical corticosteroid preparations.”

—Gray, H. R., Wolf, R. L., and Doneff, R. H.: Evaluation of Flurandrenolone, a New Topical Corticosteroid, *Arch. Dermat.*, 84:18, 1961.

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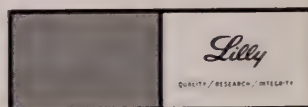
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In Memoriam

MURRAY HOWARD BASS

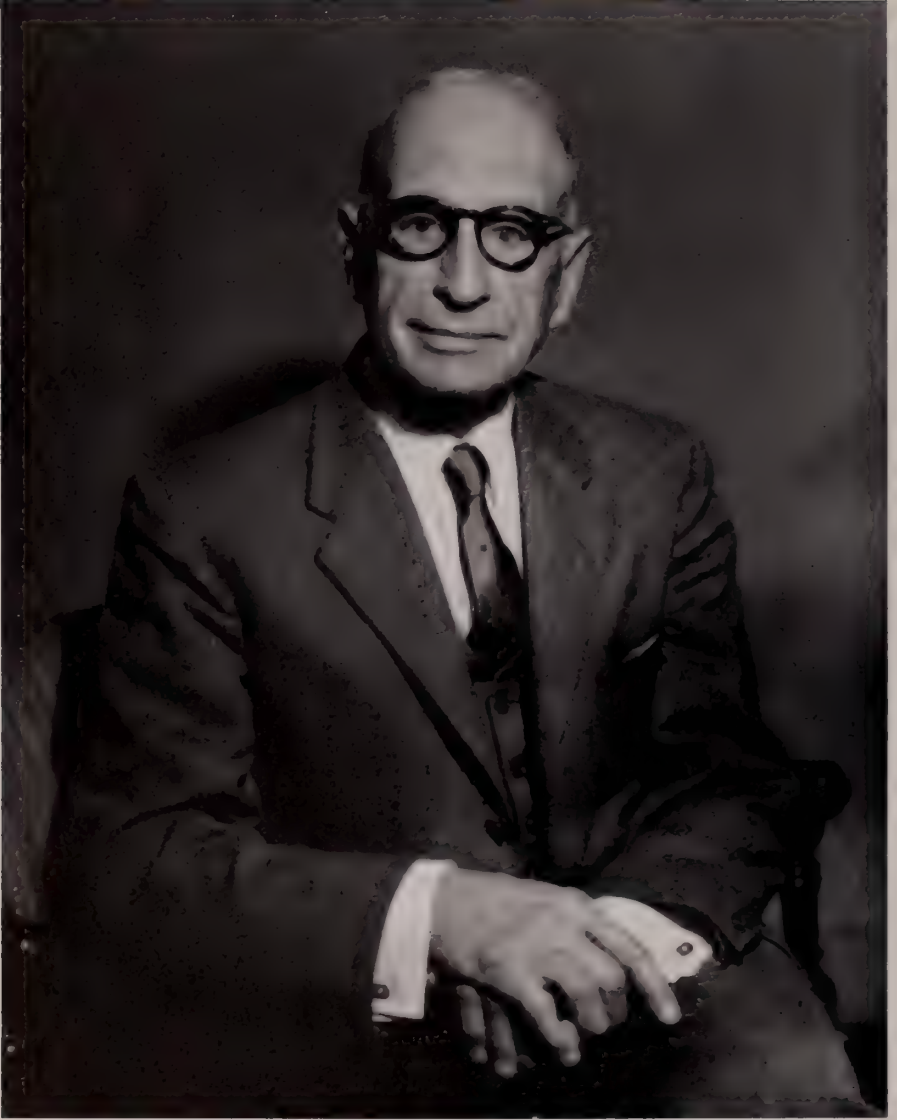
1882-1962

With his death on March 9, 1962 the worldwide fraternity of Pediatricians has lost an illustrious member, but Mount Sinai Hospital mourns the loss of one of the last in the crew which made the institution so outstanding in the first half of the century.

Murray Bass was born November 29, 1882 in New York where he received his high school education at Horace Mann School, his college and medical school instruction at Columbia University and obtained his M.D. degree in 1907. He then joined the house staff of The Mount Sinai Hospital where he spent two years. Subsequently he went abroad to Berlin and Vienna to study Pediatrics, a specialty to which he had been attracted by one of his instructors during his student years. In 1911 after his return he became chief of the clinic in the children's department of The Mount Sinai Hospital and remained associated with the Hospital until his death. He was appointed Adjunct Pediatrician in 1919, Associate Pediatrician in 1922, Attending Pediatrician and Director of the department in 1942 and Consulting Pediatrician in 1948. During all these years he gave much of his time and all of his devotion to the service of the Hospital in spite of the ever increasing demands of a private family practice and as a most called for consultant. For twenty years he functioned as a sort of executive officer of the Department of Pediatrics. After Dr. Bela Schick's retirement, he was the natural chosen successor. During the difficult years of the war and the immediate post-war period he wisely guided the department and its staff toward the transition into a full time service.

What distinguished Murray Bass from many of his contemporaries in the past as well as in the present was the harmonious allotment of his professional interests and endowments. At ward rounds and in the dispensary he was stimulating, at times brilliant but always an instructive, inspiring teacher. His gift of keen observation made him an unequaled diagnostician, his broad clinical experience a wise therapist. But the exceptional qualities of his mind did not let him rest comfortably on these accomplishments. His ever awake curiosity and his rare familiarity with auxiliary biological sciences forced him into a more penetrating analysis of his experiences as a clinician.

If one surveys the many scientific contributions of Murray Bass covering a period of fifty years one is impressed by the wide range of his interests. Orthostatic albuminuria attracted his attention in his first publications probably as a result of his contact in Vienna with Jehle of the Children's Clinic. But subsequently one can see how his scientific curiosity was stimulated by the problems arising from his own clinical experience. It would be impossible to touch even



MURRAY HOWARD BASS, M.D.
1882-1962

briefly upon the relevant articles published in all these decades. But it should be said that with advancing years his publications became more and more concerned with questions of urgent practical importance. Observations of serious acute illness attracted his attention to the dangerous idiosyncrasies of young children to metals and it was because of his penetrating analyses of cases of lead poisoning in nursing infants that the sale of nipple protectors containing this metal was prohibited in the State of New York. It was not only Murray Bass' great ability of exact clinical perception but his rare gift of correlating his observations with facts of diverse derivation which accounts for some of his most valuable contributions to pediatric practice. The clinical aspects of the RH factor published jointly with Dr. Peter Vogel, vitamin A deficiency in infants, periorbital edema as the initial sign of infectious mononucleosis are relevant examples from the later period of his scientific activity.

If we contemplate the accomplishments of Murray Bass it is not enough to pay tribute to his exemplary life. We must listen to the message he has left us and try to make it known to those of the younger generation who have confidence in us and in our judgment. Murray Bass was a great physician, one of the greatest I have ever met. His was a God given gift of a rare personality which combined qualities not often found together; love, dedication to duty and intellectual curiosity. He utilised these qualities to the fullest and he was rewarded by the love and gratitude of thousands to whom he had been a comfort in times of anxiety with his competence and wisdom. And we who were proud to have his friendship admired him because of all his qualities as a physician, but we loved him because we perceived in our contacts with him the fountain of all his achievements, the harmony and humanity which was so unique of Murray.

PAUL KLEMPERER, M.D.
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BLOOD STREAM INVASION BY UNUSUAL MICROORGANISMS

S. STANLEY SCHNEIERSON, M.D., AND CECELE HERSCHBERGER, B.S.

New York, N. Y.

A number of microorganisms of unusual interest have been isolated from blood culture in the Diagnostic Bacteriology Laboratory during the past two years. A case history of the patient from whom each organism was recovered is presented as well as salient microbiological and clinical comments. Most of these infections have been first reported within the past decade or two. During this period greater utilization of x-irradiation has prevailed and antimicrobials, steroids and antimetabolites have been introduced into clinical practice. All exert a profound physiological effect that may alter host resistance and this has undoubtedly contributed towards the appearance of such infections. None of the microorganisms presently reported, with the exception of the *Spirillum*, were among the 346 Positive isolates recovered from 5357 blood cultures taken at The Mount Sinai Hospital in the three year period of 1953-1955 inclusive (1).

GENUS ACHROMOBACTER

Case No. 1: White male, 39 years old. The patient was in apparent good health until six months ago. At that time he experienced an episode of pain on the dorsum of his left foot, without swelling or heat, which subsided spontaneously. Three months later, he began to complain of vague discomfort in the right upper quadrant unrelated to ingestion of food or exertion but relieved by rest. There was no cough or hemoptysis. He was advised by a physician that he had an enlarged heart and a murmur. Two days prior to admission, he complained of vague discomfort in his right forearm but no heat, tenderness or swelling was noted in this area. He claimed to have lost 27 pounds in the past four months. Physical examination on admission revealed an enlarged heart with a diffuse apical heave, a grade II hollow systolic murmur radiating to the axilla and a deep crescendo diastolic murmur along the left sternal border at the apex. An aortic systolic murmur of the ejection type was also heard radiating to his neck. There was minimal clubbing and no edema. Impression on admission was that the patient had rheumatic heart disease, an enlarged heart, mitral insufficiency, and aortic stenosis and insufficiency. There was no evidence of congestive heart failure. Because of his symptomatology, the persistent low grade temperature and a questionably palpable spleen, the possibility of subacute bacterial endocarditis was entertained. Eight blood cultures taken during the course of the first two weeks of hospitalization all proved negative. The patient continued to run a low grade febrile course in the hospital and complained of vague arthralgias. On the tenth hospital day, his spleen became definitely palpable. The patient was started on intravenous penicillin in large doses and intramuscular streptomycin on his sixteenth hospital day. Seven days later, while on this therapy, his temperature suddenly spiked to 103°F. and continued at an irregular spiking course for four to five days, reaching a maximum of 105°F. Blood cultures taken on three successive days during this episode were all found to be Positive for an organism identified as belonging to the Genus *Achromobacter*. A drop of exudate, obtained from the intravenous site also grew out the same organism. Antibiotic sensitivity tests revealed it to be Sensitive to tetracycline, chloramphenicol, nitrofurantoin and neomycin. Therapy was continued for five and one half weeks with penicillin and streptomycin with slow defervescence of fever. In the last month of life, congestive heart failure became the prime therapeutic problem. Temperature during

From the Department of Microbiology, The Mount Sinai Hospital, New York, N. Y.

this period was periodically and irregularly elevated to approximately 100.5 F., varying with afebrile periods. A number of blood cultures taken during this time were all sterile. His condition gradually deteriorated and he died at the beginning of the third month of hospitalization of congestive heart failure. Postmortem examination revealed adherent fibrous pericarditis. The tricuspid, mitral and pulmonic valves were found without rheumatic stigmata. The right ventricle was dilated, the left ventricle dilated and hypertrophied. The base of what remained of the aortic valve was calcific. The valve itself was almost completely destroyed but was apparently composed of three leaflets. The right cusp was replaced by red friable material and the same material partially replaced the posterior and left leaflets. Upon reconstitution of the heart no valvular material remained to effect closure of the aortic orifice. The friable vegetations encroached upon the coronary ostia but did not occlude them. No abnormalities of the coronary vessels were observed. The aorta contained several atheromatous plaques. Anatomical diagnosis was chronic bacterial endocarditis in the abacterial phase superimposed upon old rheumatic aortic valvular disease and the cause of death was attributed to chronic bacterial endocarditis with cardiac failure. Postmortem culture of the heart was Positive for *B. proteus*, *Pseudomonas aeruginosa*, *Enterococcus*; of the spleen for *B. proteus*, *Staphylococcus aureus* and *Enterococcus*. These were undoubtedly due to contamination. The organism previously recovered from the blood stream was not isolated from the heart at postmortem.

Comment

The strain recovered from the blood of this patient grew well on ordinary culture media at 37°C. under aerobic conditions. On smear, it was a small to medium sized gram-negative bacillus. In contrast to members of the family Enterobacteriaceae, it failed to reduce nitrates to nitrites or ferment glucose. Other carbohydrates were not fermented either but unlike the genus *Alcaligenes* that possesses this same characteristic, it failed to render litmus milk alkaline. It was not agglutinated by any of a number of available Herelleae or Mimeae antisera. Absence of colonial pigmentation ruled out its classification within the genus *Chromobacterium*. It was therefore identified as being a member of the genus *Achromobacter*, strains of which are widely distributed in nature and commonly found in water and soil.

Since the same organism was isolated from exudate obtained from the intravenous site, presence of a local infection there with this strain from which the organisms disseminated into the blood stream either spontaneously or as a result of penetration by an intravenous needle must be considered. However, actual bacterial contamination of the intravenous medication itself cannot be excluded as a source of the bacteremia.

CANDIDA TROPICALIS

Case No. 2: White male, 4 years old. This child was first admitted to The Mount Sinai Hospital in October, 1960, at which time a diagnosis of lymphosarcoma was made. He was treated with radiotherapy, nitrogen mustard and steroids, following which there was some recession of the cervical nodes. At the time of discharge there was no fever, anorexia or loss of weight. Cobalt therapy was started, continued intermittently, and the patient received his last treatment six days prior to the present admission in September, 1961. He was readmitted because of sudden onset of bilateral neck swelling, temperature, abdominal pain, nausea and vomiting. His temperature at the time of admission ranged from 102.2° to 104.8 F. Treatment was started with penicillin and chloramphenicol as well as with steroids. Metho-

trexate, Cytoxan and blood transfusions despite which he continued to run a high temperature and he became markedly leukopenic. A number of blood cultures taken following his admission were all negative until eight days prior to his death, at which time 2 blood cultures at two day intervals were both found positive for *Candida tropicalis*. Nose, throat and stool cultures were negative for the *Candida* but the same organism was recovered from the patient's urine. He was immediately started on intravenous amphotericin therapy. Two days prior to death the patient experienced an episode of gastrointestinal bleeding as evidenced by tarry stools. A chest x-ray taken one day prior to his death revealed extensive right lower lobe pneumonia. The patient went progressively downhill and expired. At post-mortem, evidence of fulminant leukemia and paralytic ileus of the intestine was found. Cisternal tap and intracardiac blood culture taken immediately after death failed to grow out the *Candida tropicalis*. Postmortem culture of the spleen and lung were Positive for *Candida tropicalis* but cultures of the peritoneal ascitic fluid and the ileum were Negative for this fungus.

Comment

The fungus isolated in this case was characterized by the production on Tween 80-cornmeal agar medium of a well-developed, branched mycelium bearing numerous blastospores, but unlike the more common species *Candida albicans* which produces numerous characteristic thick-walled round chlamydospores on this medium, none were observed with the strain isolated. Its identity was primarily established as *Candida tropicalis* on the basis of its carbohydrate reactions. Glucose, maltose and sucrose were fermented with production of acid and gas, whereas lactose was unaffected. This *Candida* species, along with others such as *Candida albicans*, has been isolated routinely from the nose and throat, skin, vagina and gastrointestinal tract of patients even in the absence of demonstrable disease and is ordinarily considered as a saprophyte. However, definite clinical infection and blood stream invasion with *Candida tropicalis* has been reported (2, 3), and in the latter cases as in the one herein reported, the predisposing factor of chronic, debilitating disease was present. It is often disregarded as a contaminant, but cannot be so regarded in this instance in the light of its recovery from the blood of the patient on two occasions and from the spleen and lung after death.

LISTERIA MONOCYTOGENES

Case No. 3: White male, 52 years old. The patient, a known chronic diabetic and chronic cardiac, had previously undergone a below-the-knee amputation of the right leg and an amputation of the great toe of the left foot and had suffered repeated attacks of congestive heart failure for which he was treated with digitalis and diuretics. He also was a known narcotic addict who had been "cured" fourteen years ago. Previously, he had required 5 to 10 units a day of insulin for control but for the past year he had been maintained on Orinase. He appeared to be in relatively good health until three days prior, at which time he experienced an acute episode of nausea, vomiting and anorexia. He had taken two Seconal tablets to sleep two days prior to admission but none the previous night. He had not taken any Orinase for the past seven days. On admission his blood pressure was 130/94, his pulse 88 and regular, but his respirations were Cheyne-Stokes in type. Admission temperature was 103.8 F. Examination showed nuchal rigidity and he appeared to be in impending coma. A blood culture as well as a culture of the spinal fluid were taken promptly. Examination of the spinal fluid revealed many cells, mostly polymorphonuclear leukocytes, and a 3+ Pandy reaction. No organisms were seen on stained smear of the spinal fluid. The patient was started

on penicillin, chloramphenicol and Gantresin, despite which he went progressively downhill and died the next day with apparent cardiac arrest. At postmortem, the leptomeninges covering the brain and spinal cord contained a moderate amount of purulent exudate composed of polymorphonuclear cells, macrophages, lymphocytes and considerable necrotic debris. The meningeal blood vessels showed no significant reaction. Small numbers of gram-positive bacilli were noted on stained smear in some portions of the exudate.

Comment

Results of spinal fluid and blood culture became positive after his death. The organism isolated in this case from both the spinal fluid and the blood was a small, nonsporulating, gram-positive rod with rounded ends and a tendency towards coccoid forms and shorter rods. Despite its morphological resemblance to diphtheroids which are ordinarily considered as contaminants, its identity as *Listeria monocytogenes* was suspected. To confirm this suspicion, cultures of both blood and spinal fluid were injected intraperitoneally into mice and guinea pigs with lethal results. Sections of livers of the animals revealed wide-spread areas of focal necrosis throughout the hepatic parenchyma, which areas contained small clumps of gram-positive bacilli. To further confirm its identity, the strain was instilled intraconjunctivally in a rabbit and typical corneal opacity developed. The culture was also sent to the Communicable Disease Center, Atlanta, Georgia, where Dr. Joseph H. Schubert, Chief of the Microbiology Diagnostic Unit, confirmed its identity as *Listeria monocytogenes*, Type 4B.

No history of recent or unusual contact with domestic animals by the patient was elicited from the family. *Listeria* are reported to be sensitive to chloramphenicol, tetracycline, erythromycin, penicillin and dihydrostreptomycin (4), but despite the administration of penicillin and chloramphenicol in this case, the patient's course was fulminating and fatal although treatment may have been started too late.

Much of the current literature concerned with *Listeriosis* comes from Germany where the disease is endemic (5). It has been isolated from sporadic and epidemic cases in numerous species of animals throughout the world and is responsible for infective abortion of sheep and cattle. Experimentally, intraocular instillation as well as oral administration of this organism in drinking water has been shown to produce abortion and stillbirth and early death of young rabbits (6, 7). The majority of human cases reported have occurred in the newborn and in young infants but infection in adults has also been reported (4, 8, 9). Although a number of these primary cases have occurred in apparently healthy adults, the reported cases have included those suffering from other acute and chronic diseases of varying severity, such as advanced tuberculosis, cirrhosis of the liver, hemolytic anemia, and rheumatic valvular heart disease.

MIMEAE

Case No. 4: White male, 16 years old. The patient, a known hemophiliac of four years' duration, had had bleeding in the right knee a few months previously which was gradually subsiding, but the knee became acutely painful one day prior to admission when he began to ambulate. He was seen in the emergency room where he was noted to have fever. He was admitted to the hospital and was started on sedatives, opiates for pain and fresh frozen

plasma. His fever continued and for this reason a blood culture was taken after which he was started with chloramphenicol and streptomycin. The latter, however, was discontinued the next day. His temperature persisted at levels up to 104°F. A few days later, a Positive culture consisting of gram-negative rods were found in 2 of the 3 flasks of the previously drawn blood culture. Sensitivity tests performed on these organisms revealed that they were Resistant to chloramphenicol and nitrofurantoin but Susceptible to tetracycline, streptomycin, neomycin and colimycin. Tetracycline was immediately substituted following which fever receded promptly. A blood culture taken two days after the start of the tetracycline was found to be Negative. The patient was discharged against advice six days after the initiation of therapy with tetracycline at which time swelling of the knee was less and he was afebrile. Blood taken for cold agglutinins and Streptococcus MG agglutination on admission revealed titers of 1:4 and 1:16 respectively, which is considered insignificant.

Comment

The organism isolated from this patient in 2 of 3 flasks consisted of short, plump, pleomorphic, gram-negative rods that assumed diplococcal forms on solid media. Intraperitoneal injection of the strain proved lethal to both mice and guinea pigs. Unlike members of the genus *Neisseria*, with which it may be readily confused morphologically, it grew on Endo medium and was citrate-positive. It failed to reduce nitrate to nitrite and was indol and methyl red negative. A positive catalase reaction was produced. Glucose was fermented but not sucrose, lactose, maltose and mannite. Based upon these characteristics, it was identified as a member of the tribe Mimeae. The culture, sent to S. G. Cary, bacteriologist of the Bacteriology Diagnostic Section of the Division of Communicable Diseases of the Walter Reed Army Institute of Research, was reported on the basis of agglutination with specific antiserum as being "*Herellea* Species."

The taxonomic status of the tribe Mimeae is indefinite. Organisms so classified were tentatively included within the family Parvobacteriaceae in the Sixth Edition (1948) of Bergey's Manual but are not included at all in the latest, Seventh Edition (1957) of this manual. The designation Mimeae, first proposed by De Bord in 1942 (10), is derived from the ability of members of this tribe to "mimic" other organisms, particularly *Neisseria*, in morphology, staining reactions and cultural characteristics. A gonorrheal-like urethritis caused by the Mimeae which are relatively resistant to the action of penicillin has actually created diagnostic and therapeutic difficulties (11). De Bord included three genera within this tribe, namely, Mimeae, *Herellea*, and *Colloides*. Differentiation among the genera is based upon their reactions with different carbohydrates. Mimeae polymorpha fails to ferment carbohydrates. *Herellea vaginicola* produces acid from glucose, galactose, xylose and arabinose whereas *Colloides anoxydana* produces acid and gas from glucose, maltose, lactose, mannitol and dulcitol. In view of its carbohydrate fermentations, growth on citrate and its agglutination by *Herellea* species antiserum, the strain involved in this case was identified as *Herellea vaginicola*. Another similar organism, *Bacterium anitratum*, has been shown to be physiologically and morphologically related to Mimeae (12) and has also been reported as being the causative agent of clinical meningitis (13). Members of the tribe Mimeae have been recovered from river water (14) and from a variety of human sources (15), including vaginal, urethral

and conjunctival secretions, war wounds, burns, chaneroid lesions, the urine, ear and respiratory tract secretions, blood, the brain, meninges and spinal fluid, petechiae, bone marrow and synovial fluid and from healthy normal people as well. Although the actual pathogenicity of *Mimeae* has been subject to question in view of their widespread distribution in nature and in normal body cavities, these organisms have been definitely incriminated in certain infections, some of them severe and even fatal. Among these are included urethritis (11), meningitis (15), septicemia (16), and bacterial endocarditis (17, 18).

SHIGELLA SONNEI

Case No. 5: White female, 82 years old. This patient had a twenty-five year history of diabetes, arteriosclerotic heart disease, and systolic hypertension. Five months prior to admission, she suffered her first of several strokes. Her diabetes was apparently well controlled until three days prior to admission at which time her temperature suddenly spiked to 105°F. and she had frequent, foul-smelling, watery stools. One day prior to admission she became progressively more lethargic. She was believed to be in ketosis and was transferred to the hospital in a comatose state. On admission her urine showed 4+ sugar and 3+ acetone. She was promptly treated by hydration, intravenous and intramuscular insulin and because of her persistent temperature a blood culture was drawn which proved positive in all flasks for an organism identified as *Shigella sonnei*. After the blood was drawn for culture, she was immediately started on penicillin, streptomycin and chloramphenicol. Subsequent blood cultures all proved to be negative. Her temperature responded rapidly, her diabetes gradually came under control, and she was discharged to be cared for in a nursing home after what was considered a satisfactory therapeutic response. Antibiotic sensitivity determinations performed on the organism isolated from the blood proved it to be Sensitive to chloramphenicol, tetracycline, neomycin and nitrofurantoin but Resistant to streptomycin.

Comment

The gram-negative, nonlactose fermenting, nonmotile organism recovered from the blood of this patient was identified as belonging to the species *Shigella sonnei* on the basis of its morphology and chemical and serological reactions. This identification was corroborated by the Bureau of Laboratories of the Department of Health of the City of New York. Infection with *Shigella* is not widespread in nature and is generally limited to man and perhaps apes and monkeys kept in captivity. The portal of entry is oral, usually by means of infected fingers, food or water, after which the gastrointestinal tract becomes involved. A bacteremic phase in Shigellosis, in contrast to Salmonellosis, is extremely rare but does occur occasionally involving the species *Shigella dysenteriae* or *Shigella flexneri*. Felsen in a review of published reports of Shigellosis from 1900 to 1945, found 34 cases of *Shigella* bacillemia but in not one single instance was *Shigella sonnei* involved (19). One case of bacteremia with this organism, however, has been recently reported by Tatham and Williams, who found one positive blood isolate of *Shigella sonnei* following blood culture performed on seven children with sonnei dysentery (20).

SPIRILLUM

Case No. 6: White male, 72 years old. The patient was first admitted to The Mount Sinai Hospital in 1957 because of loss of energy and breathlessness on exertion. A diagnosis of

pancytopenia due to erythroleukemia was made and the patient was treated with repeated blood transfusions and 20 mg of prednisone daily, following which he was discharged to the Hematology Clinic for observation and treatment. He was periodically readmitted to the hospital primarily for treatment of his hematological status. On the occasion of one brief admission in February, 1959, a fever of 103.4°F. was noted. Numerous ecchymoses and petechiae were present. On this occasion he was treated with penicillin, 1 million units daily, and 1 Gm of streptomycin as well as with hydrocortisone hemisuccinate, after which the temperature subsided. Numerous blood cultures taken during this admission were sterile, except for one which was reported as "Spirillum." He was again admitted in November, 1959, because of cough and fever of one day's duration and a maculopapular eruption over the chest, back and legs. Five blood cultures taken at this time were reported as sterile. He entered the hospital again in March, 1960, because of anorexia, fever and diarrhea of several days' duration. He had been receiving transfusions at the rate of one every 1-2 weeks. During this admission, five blood cultures taken all grew out a spirillum organism. The organism could not be recovered from the nose, throat, urine or stool. Treatment consisted of transfusions and penicillin 1.6 million units and tetracycline 2 Gm daily. The temperature gradually subsided over the next four days and remained normal for the remainder of his hospital stay. Serial blood cultures taken after the second week of antibiotic therapy were all negative and when he was discharged he was asymptomatic and afebrile. His final admission, in August, 1960, was because of fever, anemia, and marked disorientation. The chest was clear, the heart appeared enlarged and the liver was enlarged to six fingerbreadths below the right costal margin. His spleen was not palpable. The patient was treated with steroids as usual, repeated transfusions and antipyretics. About seven to ten days after admission the patient became increasingly uncooperative, depressed and attempted to climb out of bed. The impression of the neurological service at this time was that the patient had diffuse encephalopathy. His hemoglobin had to be maintained with repeated transfusions of which he received several hundred in the course of his prolonged illness. Shortly before his death, the patient began to run increasingly high fever to 104°F. and became moribund and died on August 30, 1960. Repeated blood cultures during this admission as well as one spinal fluid culture were all sterile. No autopsy was obtained.

Comment

The gram-negative spirillum isolated in this case grew well on the regular liquid and solid laboratory media, with or without blood, at 37°C. under both aerobic and microaerophilic conditions. It was culturally and morphologically similar in all respects to that previously described by Schwartzman, *et al.* (21). Antibiotic sensitivity tests revealed it to be Sensitive to erythromycin, chloramphenicol, tetracycline, polymyxin and nitrofurantoin, Moderately Resistant to penicillin, streptomycin and neomycin and Resistant to vancomycin, novobiocin and Gantrisin.

This case is included among the cases reported by Kowal in a review of the literature of severe systemic infections caused by members of the species *Spirillum* (22). Unlike *Spirillum minus*, the etiological agent of rat bite fever, the organism recovered in this case grows readily on artificial media. Some question has arisen as to the relationship between *Spirillum* and *Vibrio fetus*, a case of which is subsequently reported. Although a number of short, comma-like forms were observed on smear of the culture obtained from the blood of this patient, its predominant morphology was elongated and spirillar, not only in the original culture, but in numerous subcultures as well. Organisms belonging to the Genus *Spirillum* exist widely in nature. They are usually in fresh and salt water con-

taining organic matter and thus ample opportunity for exposure to these organisms is readily afforded. Differentiation between *Spirillum* and *Vibrio fetus* is further discussed in connection with the following case.

VIBRIO FETUS

Case No. 7: White female, 76 years old. The patient had fifteen previous admissions to The Mount Sinai Hospital since 1945 because of sprue and malabsorption syndrome which was not corrected by diet and was only partially responsive to steroids. For the past few months, she had had persistent pain in the right lower extremity, localized around the outer aspect of the right knee. This followed an episode described as herpes zoster. Pain had been persistent and unremitting in nature and was relieved only partially by narcotics. Paravertebral block and hypnosis provided no relief. Her present admission was for diagnosis and treatment of the persistent severe pain in the region of the right knee and because of a fever of 103 F., slight dyspnea and chills of two days' duration. Her right knee joint was aspirated on admission and about one cc of straw-colored, viscous fluid, contaminated with a small amount of blood, was obtained. No white blood cells or organisms were seen on smear and culture of the synovial fluid resulted in the isolation of *Staphylococcus albus*, which was a contaminant in all probability. Pain in the knee persisted for the next ten days. On the eleventh day following the initial tap, the patient was suddenly seized with a shaking chill and a rise in temperature to 105.2°F. A significant drop in blood pressure from 110/70 to 85/50 was noted. Blood culture taken at this time grew out an organism on all media which was identified as *Vibrio fetus*. One Gm of tetracycline was administered intramuscularly and by the next day her temperature had returned to normal. The antibiotic was continued for four days during which time her temperature was essentially normal and remained so thereafter, except for occasional rises to 101°F. at three to seven day intervals and lasting for only one day. Subsequent blood cultures were all sterile. She remained in the hospital for about one month during which time her condition remained essentially unchanged. About one month after the febrile episode and chill, the patient became lethargic, drowsy and appeared very weak and suddenly vomited about 100cc of guaiac positive material and expired. At postmortem, culture of the peritoneum and spleen grew out a variety of enteric bacteria but the *Vibrio fetus* strain was not isolated.

Comment

The organisms recovered from the blood were small, slender, gram-negative, comma-shaped rods that grew well on blood agar, glucose broth, yeast broth and Brewer's thioglycollate medium at 37°C. As contrasted with the organism isolated in the previous case, the characteristic vibrio morphology persisted on repeated subculture and spirillar forms were observed but rarely. Because of this, the strain was reported as "*Vibrio fetus*." Serological confirmation of its identity was obtained from E. O. King of the Microbiology Diagnostic Unit of the Communicable Disease Center, Atlanta, Georgia.

Vibrio fetus is an important cause of infectious abortion in such common domestic animals as cattle and sheep but despite its widespread prevalence in nature, reports of human infection with this organism have been relatively uncommon considering the vast opportunities for such infection. A number of recent reports (23-25), however, attest to either an increased incidence of such infections or a greater awareness of its possible occurrence. Successful therapeutic results have been reported with chloramphenicol, chlortetracycline and with combinations of dihydrostreptomycin and tetracycline and of penicillin and

sulfonamide, but not with penicillin alone (25). Although individual strains vary in their antibiotic susceptibility, the strains involved in the reports cited have been sensitive to one of the tetracycline compounds as was the strain isolated in this case. Some question has arisen as to the possible relationship between strains designated as *Spirillum* and *Vibrio fetus*. Both may actually be the same organism. According to Bergey, both are included within the family Spirillaceae, and are differentiated chiefly on the basis of their morphology. *Vibrios* are short and vibrio-shaped whereas the spirilla are elongated, filamentous and spiral. Both forms, however, may be present in a single culture and thus create considerable difficulty in classification. This dilemma is illustrated in the case reported by Jackson *et al.* (26) who first considered their organism to be a *Spirillum* and then changed its designation to *Vibrio* after it was found to agglutinate with a known *Vibrio fetus* antiserum. If both species possessed a common antigen, however, they would both be reactive to the same antiserum and this possibility cannot be excluded. It is of interest that a serological relationship has been demonstrated between *Vibrio fetus* antiserum and such heterologous species as *Salmonella pullorum* and several *Brucella* species (27). Further studies are indicated before the relationship, if any, between *Spirillum* and *Vibrio fetus* is satisfactorily clarified.

DISCUSSION

Ability of a microorganism to cause infection or invade the blood stream is a function of its virulence in relation to the resistance of the host towards its presence. Many factors are involved in the latter, among which may be included the activity of the reticuloendothelial system, phagocytosis by peripheral polymorphonuclear leukocytes, the presence or absence of natural or acquired protective antibodies, the bactericidal action of the serum as well as its complement and lysozyme content. All these body defense factors may be adversely affected by x-irradiation, the administration of steroids, antibiotics, antimetabolites, as well as by the presence of chronic debilitating disease, hematologic disorders, metabolic disturbances and malignancy. Under propitious circumstances even such ubiquitous laboratory contaminants as *B. subtilis* (28, 29) and *Diphtheroids* (30), which are usually considered as being innocuous, may be responsible for septicemia. A number of the cases in these last reports were suffering for one or another of the diseases noted above. In the light of this situation, any classification of a particular species of bacteria as being saprophytic or as pathogenic has lost much of its clinical validity and all organisms must be considered in relation to the status of the host and the integrity of his defense mechanism to resist invasion.

All the microorganisms isolated in this study, with the exception of *Shigella sonnei*, exist freely in nature, among domestic animals, as part of the normal flora of various human body cavities, in soil and in water, so that opportunity for human exposure to them is widespread. In view of the paucity of cases attributed to them, a basic lack of virulence on their part must be generally assumed except under the special circumstances considered above. The patients

reported on were all involved with concomitant disease of varying severity and this undoubtedly contributed to the resultant breakdown of their defense mechanisms that permitted these "non-pathogenic" organisms to disseminate into their blood streams and even produce a fatal outcome in one instance, that of *Listeria monocytogenes*. Deaths of the other patients who succumbed, however, were attributable to their primary disease rather than to invasion of their blood streams.

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THE PSYCHIATRIST IN A GENERAL HOSPITAL

HIS FUNCTIONAL RELATIONSHIP TO THE NON-PSYCHIATRIC SERVICES

STANLEY BERNSTEIN, M.D., AND M. RALPH KAUFMAN, M.D.

New York, N. Y.

The historical development of psychiatric units in general hospitals is of great interest in relation to the psychiatrist's role. Psychiatric units and psychiatrists in general hospitals have been functioning for a great many years. What has changed, however, is the basic philosophy of their utilization.

Within the past ten years there has been a remarkable increase in the number of such psychiatric units in general hospitals, so that 337 new psychiatric services were opened during this period of time as compared to 10 units from 1901-1915, 18 units from 1916-1925, and 75 units from 1926-1945.

In the early days a psychiatric unit in a general hospital functioned essentially as a "psychopathic" pavilion, geographically located within the complex of the general hospital. In this capacity it might have been operated as a receiving unit or as that part of the hospital to which disturbed and unmanageable patients were transferred. The psychiatrist, when he was utilized, was called in to confirm the already made diagnosis of psychosis or other types of disturbed behavior which made the patient unmanageable on whatever service that he happened to be. The psychiatrist's role was that of a transportation officer, since he was familiar with the legal rigamarole which enabled the patient to be taken from the medical or surgical ward and transferred to a psychiatric unit for further management.

This essentially represented the psychiatrist's role in medicine as practiced in a general hospital for many years; that is, provided he was granted even such minimal privileges in relation to a general hospital. With the increasing recognition of the role of psychiatry as a basic science in medicine, and with the increasing acceptance of the patient as a person, amongst other things, the psychiatrist's role has begun to change. Today the psychiatric unit and the psychiatrist by and large serve a completely different function than they did in the early days. The psychiatrist has become functionally and operationally a member of the medical team, and his professional advice is sought and utilized from this point of view.

At The Mount Sinai Hospital since 1946 a Department of Psychiatry has functioned within the framework of this philosophy of the practice of medicine. One division of the Department of Psychiatry is the Division of Liaison Psychiatry, which includes the assignment of a team of psychiatrists to each service. These psychiatrists are essentially functioning members of the particular department to which they are assigned.

As an illustration, the Department of Medicine has at least four such psychiatrists assigned to it. The role of the liaison psychiatrist is a multiple one. He

From the Department of Psychiatry, The Mount Sinai Hospital, New York, N. Y.

functions as a consultant, teacher, and member of the medical team. His relationship to the department is such that he is accepted in all these capacities. He is free to see any patient who is admitted to the Medical Service whether there is an official request for consultation or not. He works with the attending staff, the resident and intern staff, the nurses, social service, or any of the other members of the Medical Department. He participates in ward rounds, clinical teaching, and individual teaching at all echelons.

It is the intent of this paper to present experiences in relation to the spectrum of the problems confronting a psychiatric service in this area. The integration of psychiatry with medicine as a whole has facilitated the work of the psychiatrist in such a setting in a general hospital. The administrative routine which has been followed somewhat loosely in our hospital when a consultation is necessary, is to request from the parent service on a special consultation slip which contains the name of the patient, the reason for the request in terms of the problem presented and the primary diagnosis, and for the opinion of the consultant.

The reason why the statement is made that the procedure has been followed rather loosely is to indicate the fact that since the psychiatrist functions as part of the service to which he is assigned, in many instances he fulfills his function without any formality, and therefore the only record of this service may be a brief note on the chart or a verbal discussion with the house staff or the attending staff. Therefore, it should be understood that the figures for the number of consultations as recorded in the Psychiatric Service record book do not represent the absolute figure of such consultations. In addition, the consultation slip when it is made a record usually involves only the first consultation and very frequently does not include any follow-up interviews or procedures.

We were interested in obtaining data concerning a number of factors involved in this liaison service. For instance, the knowledge as to the type of case in which the psychiatrist's consultation and advice was requested seemed to us to be one index of his role as visualized by the parent service. In order to obtain this information, an analysis was made of our records, and the data as to the primary diagnoses of the patients seen by the psychiatrist was noted. Our findings will be presented initially in terms of statistics. Table I indicates that in approximately ten per cent of all admissions psychiatric consultations were formally requested. The Medical and Orthopedic Services were in the range of twenty per cent of their patients, while the Obstetrics and Gynecology Service requested consultation for approximately four per cent of their patients. The timing of the requests in relation to the number of days the patient was in the hospital showed a striking parallel to the number of consultations requested. Psychiatric consultation was accomplished, on the average, 9 days after admission; on the Medical Service 5 days, the Orthopedic Service 7, and the Obstetrics and Gynecology Service 14.

Table II is an evaluation of the psychiatric consultations in regard to the action taken by the liaison psychiatrists. One is immediately impressed by the relatively small number of patients that cannot be handled in a general hos-

pital, which is 98 out of a total of 20,011. These data again illustrate the importance of the Social Service Department; the figure of 340 patients is only an indication of the primary disposition of the patient. Many more patients utilized Social Service facilities as an adjunct to psychiatric therapy.

The type of psychotherapy given to patients was arbitrarily divided by the authors into "brief" and "intensive" therapy. Brief therapy included those instances in which the patient was seen one to five times, and dealt with reassurance, catharsis, education, manipulation of environment, etc.

TABLE I
Incidence of Psychiatric Consultations. (Two Years)

Service	Total Admissions	Psychiatric Consultations Requested
Medicine	3743	617
Surgery	2858	293
Neurology and Neurosurgery	756	112
Obstetrics and Gynecology	99	
Enterology	3140	
Ophthalmology	1437	157
Orthopedics	323	19
Urology	281	23
Dermatology	375	53
	753	36
	46	9
	13,811	1319

TABLE II
*Action taken by Liaison Psychiatrists in 2309 Psychiatric Consultations over a
Three Year Period*

Admitted to Psychiatric Ward	144
Referred to Psychiatric Clinic	408
On Service—Psychotherapy*	825
Referred to Social Service	340
Transferred to State Hospital	98
Observation Only, No Recommendations	494

* On Service Psychotherapy consisted of both brief and intensive therapy. Brief therapy (687) was limited to five sessions or fewer and dealt with superficial problems of adaptation. Intensive Therapy (138) consisted of more than five sessions and was "insight oriented."

Intensive therapy was usually more than five sessions and was more "insight oriented." Those cases where it was felt that additional benefit could be obtained by treatment in a "psychiatric setting" were transferred to the psychiatric ward, *i.e.*, instances in which there was a management problem, where the psychopathology was of acute importance or where psychiatric nursing was deemed essential. It is noteworthy that only a relatively small number of patients could not be treated effectively on the parent service and was transferred to the Psychiatric Service.

The major emphasis of this study was the type of case in which the psychiatrist's consultation and advice were requested. Tables III-VII are a breakdown of the consultations by service.

The Medical Service, during the period of time under study, requested 617 consultations (Table III). Of this number 144 or 23 per cent were of the category that previously represented the "psychiatrist's domain"—these included uncooperative patients, psychoses, senile confusion and drug addiction; 473 or 77 per cent of the consultations indicated a new role and utilization for psychiatrists in a general hospital. This role was that of an active participant on the medical team. The concept of the psychophysiological unity of the organism was put into practice rather than being paid lip service. In 32 cases the request asked the psychiatrist to help in the differential diagnoses. These requests were for the purpose of arriving at a positive diagnosis, in other words, specific emotional constellations that were responsible, if there were any, for the patient's problems. The internist apparently is no longer satisfied to make a psychiatric diagnosis on the absence of organic findings.

The greatest number of consultations, over seventy per cent, involved problems confronting the referring physician which were not on an "either-or" basis. The physician did not ask for an organic or psychological differentiation. He asked what role emotional factors were playing in either the causation, perpetuation or exacerbations of the medical problem, and by inference what role emotional factors should play in therapy.

As Table III indicates involvement of the gastrointestinal and cardiovascular systems were prominent in presenting problems which led to consultations. Was this ulcerative colitis being provoked or perpetuated by emotional factors? Could this patient benefit from psychotherapy as well as or in addition to colostomy? How would he react to a colostomy as far as his subsequent adaptation to society? How about large doses of cortisone and the possibility of a resultant psychoses? Would he be a suitable member for the colostomy club? Is preoperative psychotherapy indicated in terms of the mutilation?" Similarly with ulcer patients, requests were in terms of how can we keep him on his diet, could his attacks be related to arguments with his wife, to his struggles in business and how can we start preparing the patient for discharge, a period of frequent relapses?

Almost equal in frequency were consultations where the presenting complaints were involvement of the cardiovascular system, as "Blood pressure down, how can we help keep it down; coronary thrombosis with severe reactive depression; what could the physical illness mean to the patient in terms of sexual potency with which he is obsessed; a peripheral vascular disease, marked anxiety causative or reactive?"

Two other medical problems were frequently presented to the psychiatrist from the Medical Service, namely, asthma and diabetes. Asthma cases frequently appeared in terms of helping the patient to separate from the hospital, exaggerated fears of suffocation or death, asthma apparently provoked by the visit of a significant person, or asthma apparently alternating with depression.

TABLE III

Medicine: 617 Consultations

<i>I. Involvement of Cardiovascular System—142</i>
Tentative Service Diagnosis
Congenital—5
Anginal Pain—63 (48 Innocent)
Coronary Thrombosis—16
Rheumatic Heart Disease—4
Essential Hypertension—34
Arrhythmias (sinus tachycardia)—10
Peripheral Vascular Disease—10
<i>II. Involvement of Gastrointestinal System—173</i>
Tentative Service Diagnosis
Ulcerative Colitis—45
Peptic Ulcer—38
Regional Ileitis—12
Hepatitis—4
Pancreatitis and Gall Bladder—11 (Biliary Dyskinesia)
Esophageal Spasm—1
Pylorospasm—14
Gastritis—26
Mucous Colitis—10
Pruritus Ani—4
<i>III. Involvement of Respiratory System—36</i>
Tentative Service Diagnosis
Asthma—26
Bronchitis—2
Tuberculosis—2
Pneumonitis—6
<i>IV. Metabolic Diseases—37</i>
Tentative Service Diagnosis
Diabetes—21
Thyrotoxicosis—13
Obesity—2
Hypothyroidism—2
ACTH Reaction—9
<i>V. Involvement of Skin and Musculoskeletal System—18</i>
Tentative Service Diagnosis
Neurodermatitis—3
Pemphigus—1
Urticaria—1
Arthritis, Rheumatoid—13
<i>Others</i>
1. Management of Uncooperative Patient—54
2. Different Diagnosis—32
3. Suicidal—20
4. Patient request (Ulcerative Colitis—14)—35
5. Drug Addiction—16
6. Senile Confusion—24
7. Miscellaneous (Hysteria, Schizophrenia, etc.)—30
Total—211

The diabetic cases were principally in the juvenile or older age group where the consultations dealt with problems of getting the patient to take his medications, or defiance and rebellion problems in juveniles apparently related to relapses.

Table IV represents consultations received from the Surgical Service. Here the

TABLE IV
Surgery: 293 Consultations

<i>I. Preoperative Opinions as to Scheduling of Operation</i>		<i>24</i>
Ulcerative Colitis	5	
Sympathectomy	2	
Ulcer	4	
Thyroid	4	
Regional Ileitis	2	
Diabetic Amputation	7	
<i>II. Preoperative Anxiety and/or Depression</i>		<i>44</i>
Ulcerative Colitis	3	
Malignancies (confirmed and suspected)	27	
Diabetes	8	
Ulcer (Gastrectomy)	6	
<i>III. Differential Diagnosis—Hypochondriasis</i>		<i>33</i>
Assistance in diagnosis of hysterical pain (abdomen, back, chest, etc.)		
Complaints far beyond physical symptoms		
<i>IV. Postoperative Reactive Depression</i>		<i>74</i>
Ulcerative Colitis	9	
Cholecystectomy	5	
Ulcer	8	
Thyroid	6	
Malignancy	46	
<i>V. Postoperative Management Problem and Psychotic Reaction</i>	(67)	<i>72</i>
Diabetes	(15)	
Amputation	6	
Malignancy	4	
Thyroid	52	
Peptic Ulcer	2	
	8	
<i>VI. Preoperative and Postoperative Working Through (Congenital Cardiac)</i>		<i>10</i>
<i>VII. Toxic Psychoses</i>		<i>21</i>
Alcohol	3	
Drugs	12	
Illness	6	

psychiatrist also was considered an integral member of the surgical team and was utilized in many areas.

1. In relation to surgery he was called in before operation to evaluate the patient's capacity to tolerate the surgical procedure, or to work with the anxiety or depression already overt. Similarly, in postoperative cases he was consulted in regard to anxiety, depression or any difficulties in adapting to subsequent rehabilitation.

2. The psychiatrist was also asked to help in many of the problems of differential diagnosis, particularly where the complaints did not correlate with physical symptoms.

3. The question frequently posed to the psychiatrist was of the patient's emotional ability to tolerate certain drugs and to assist when a toxic reaction did occur.

TABLE V
Obstetrics and Gynecology: 157 Consultations

<i>A. Evaluation of Emotional Factors; Menometrorrhagia</i>		35
<i>B. Evaluation of Emotional Factors; Hyperemesis Gravidarum</i>		14
<i>C. Evaluation of Multiple Functional Complaints</i>		14
<i>D. Reactive Depression</i>		24
Ovarian Tumor	3	
Kraurosis Vulvae	1	
Fibroids	15	
Carcinoma of Pelvic Organs	4	
Myotonia	1	
<i>E. Preoperative Evaluation of Anxiety and Contraindications</i>		23
Cervix Polyps	3	
Fibroids and hysterectomy	15	
Cystocele	2	
Carcinoma of Uterus	3	
<i>F. Postoperative Management and Evaluation</i>		22
Postpartum	8	
Dilatation and Curettage	7	
Diabetic	1	
Salpingo-oophorectomy	3	
Hysterectomy	3	
<i>G. Management: Frank Psychiatric Pictures</i>		19
Schizophrenia	14	
Psychopathic Personality	1	Uterine Bleeding
Neurosis	2	Stress Incontinence
Toxic Psychosis	2	Vulvovaginitis Dilatation and Curettage Preoperative
<i>H. Miscellaneous</i>		6
Psychic factors in sterility	3	
Psychic urinary retention	3	

Tables V, VI, and VII, covering the Obstetrics and Gynecology, Neurology, and Urology, Skin and Enterology services are self explanatory.

CASE REPORTS

Case 1. The patient is a sixteen year old white, Jewish, unmarried female, rather attractive but somewhat hostile and negativistic, who was referred by the Neurological Service for a psychiatric consultation. She had a three month history of six episodes of fainting, with complete loss of consciousness, insomnia, anorexia, difficulty in vision and marked memory difficulties. On the Neurological Service a complete work-up including skull x-rays, encephalogram, visual fields, and clinical neurological tests did not reveal any abnormality.

It was noted by the neurologist on the ward that the patient would experience a marked

exacerbation of her symptoms in relation to visits of her mother. The psychiatric consultation disclosed that the patient had evidence of marked emotional conflicts and she was transferred to the psychiatric ward. From the onset of the patient's admission to the Psychiatric Service, she developed an intense, erotic transference to the therapist, and within a period

TABLE VI
Neurology: 112 Consultations

<i>A. Differential Diagnosis</i>		35
Anorexia and dysphagia	4	
Brain Tumor	6	
Causalgia	4	
Encephalitis	4	
Abdominal Pain	6	
Vertigo and Headache	5	
Hypochondria	6	
<i>B. Evaluation of Emotional Overlay of Original Illness</i>		40
Lumbar postpartum	6	
Multiple Sclerosis	4	
Reactive Depression	16	
C.N.S. Depression	4	
Parkinsonism Depression	2	
Acromegaly	1	
Myotonic Atrophy	1	
Neuralgia	2	
Poliomyelitis	2	
Pituitary Adenoma	2	
Cerebral Cord Lesion	2	
Meningoencephalitis	3	
<i>C. Evaluation of Overt Psychiatric Conditions</i>		33
Schizophrenia	5	
Conversion Hysteria	4	
Suicide	3	
Alcoholism	2	
Organic Mental Syndrome	10	
Behavior Problems	3	
Barbiturate Intoxication	5	
<i>D. Evaluation of Mental Status</i>		14
Spinal Tap Reaction	2	
Head Injury	3	
Convulsion	2	
Cerebral Concussion	2	
Mental Deficiency	5	

of four days, she revealed a three year history of seven suicidal attempts. The last "suicidal gesture" culminated in taking an overdose of Dilantin® which she had received from the Neurological Outpatient Department. The overdose of this medication it was felt had led to her presenting symptoms. During the course of her stay in the hospital, the patient gradually gave up her somatic complaints as the emotional difficulties came to the foreground. Within a period of three months, the patient was discharged to the Psychiatric Outpatient Department where she continued to make good progress in relation to working through her interpersonal difficulties.

Cases 2 and 3. These cases illustrate the efficacy of superficial psychotherapy directly on the parent service.

A male patient, thirty-two years of age, who was convalescing from a successful subtotal gastrectomy refused to get out of bed and take his prescribed medications. He began to have many of his "ulcer symptoms," accompanied by a good deal of anxiety. The psychiatrist on the ward learned in a relatively short period of time that the patient was frightened by the idea of his return to health with all its attendant responsibilities. Two subsequent interviews

TABLE VII
Urology, Skin and Enterology Consultations

<i>I. Urology</i>	36
A. Management	
Denial, lack of cooperation	15
B. Reactive Depression Incontinence	13
C. Preoperative Evaluation Elective Surgery (Hypospadias)	3
D. Anxiety, Differential Diagnosis Hypochondriacal	3
E. Postoperative Reaction Paranoid	2
<i>Psychiatric Findings</i>	
Paranoid Reaction	6
Reactive Depression and Hysteria	16
Schizophrenia (acute)	13
Organic Mental Syndrome	1
No Psychiatric Findings	0
<i>II. Skin</i>	9
A. Psychiatric component	
Neurodermatitis, atopic, dermatitis herpetiform	4
B. Reactive Depression and Anxiety	
Erythema Multiforme, scleroderma pemphigus	5
<i>Psychiatric Findings</i>	
Schizophrenic	3
Character Neurosis	2
Reactive Depression	2
No Psychiatric findings	2
<i>III. Enterology</i>	19
A. Menière's Syndrome	5
B. Suicidal Attempts	3
C. Differential Diagnosis, Globus Hystericus, dysphagator	3
D. Preoperative Evaluation	2
Menière's	
Rhinoplasty	
E. Reactive Depression and Anxiety	6

with the psychiatrist served to allay some anxieties of the patient and enabled him to co-operate with medical orders.

The other case was of an eighteen year old female patient admitted to the hospital because of headaches and diplopia. She had been unable to verbalize certain hostile feelings towards her mother. Three psychiatric interviews plus completely negative medical studies enabled her to accept the emotional basis of her troubles. Rather than face long-term psychotherapy, she made a flight into health (leaving the hospital symptom-free and determined to "get things off her chest" with regard to her mother)

Case 4. This case illustrates the role of psychogenic factors in medical illnesses attesting again to the fallacy of the either-or approach (an illness has to be organic or functional).

A fourteen year old white, Jewish male was admitted for the second time to the Medical Service for an acute flare-up of ulcerative colitis including weight loss, bleeding, spasm, tenesmus and diarrhea. After one month he responded well to cortisone and other medication. He was discharged but suffered a total relapse one day later with massive bleeding diarrhea and returned with his previous symptoms. He was readmitted to the Medical Service, where it was felt that psychiatric intervention might be helpful in the total management of the case.

On the Psychiatric Service, the patient entered rather willingly into psychotherapy, which was principally supportive and re-educative and was assisted greatly by Social Service department work with the mother and father. After two months on the ward, the patient was discharged, and a two year follow-up has revealed no relapse.

SUMMARY AND CONCLUSIONS

The functional role of the liaison psychiatrist in a general hospital, as visualized by the parent services, was the focus of this study. Utilizing our consultation requests as one index of this role, our findings can be summarized as follows:

The traditional role of the psychiatrist in a general hospital as "transportation officer to a mental institution" has undergone a striking change. In our series less than eight per cent of the consultations dealt with "unmanageable cases."

Our study indicates however, that the psychiatrist has been asked to become an integral member of the medical team. Sixty-five per cent of our consultations requested the psychiatrist to evaluate the role of the emotional factors in the causation, perpetuation or exacerbation of the medical problem; and by inference to what extent psychotherapy or other psychiatric treatment modalities should be included in the total therapy. These consultations indicated a greater degree of sophistication and understanding in regard to psychiatry. The fact that emotional conflicts and disturbances are always present in varying degrees was accepted; the question posed was in terms of the specific relation of these conflicts to the dysfunction.

The remaining 27 per cent of the consultations requested specific assistance in therapeutic measures. The problem of choice of drugs, *i.e.*, cortisone with an evaluation of the "psychotic-potential," preoperative and postoperative anxiety and/or depression in regard to surgical procedures, and preparation for discharge from the hospital illustrate this role of the psychiatrist. The question of a differential diagnosis between an "organic" or "functional" illness was infrequent. It seems to have become quite well recognized in this hospital that this kind of dichotomy is a reflection of the frame of reference of the physician, rather than the problem of the patient.

The operational relationship of the psychiatrist to the non-psychiatric services in a general hospital will be described in a subsequent paper.

REFERENCES

1. Psychiatric Units in General Hospitals (1954-1958)—Fact Sheet #13, Joint Information Service of American Psychiatric Association and National Association for Mental Health.

ANCILLARY TECHNIQUES IN THE INVESTIGATION OF CHRONIC LUNG DISEASE*

LOUIS E. SILTZBACH, M.D.

New York, N. Y.

All of us are aware that patterns of chronic lung disease have been undergoing an important change in this country and elsewhere. The remarkable effects of the antituberculosis drugs on the mortality and incidence of tuberculosis have been borne in upon us, and the almost equally brilliant effectiveness of penicillin in forestalling the development of lung abscess and its sequelae, empyema and bronchiectasis, has been another gratifying development.

As a result, chest clinicians now find themselves increasingly concerned with chronic and, in the main, noninfectious pulmonary diseases of the middle and older age groups; particularly cancer of the lung, chronic bronchitis and emphysema, and pulmonary embolization. At the same time, other lung diseases once rare have increased alarmingly. A sharp rise in disseminated fungal infections has followed wide-scale use of antibiotics and corticosteroids, and of new cytotoxic agents for the treatment of malignant neoplasms.

It is the intention of this communication to examine several diagnostic techniques which the chest physician currently has at his disposal for the investigation of chronic lung disease. For the most fruitful application of these diagnostic techniques we can consider it axiomatic that a careful history and physical examination with the customary laboratory and radiologic studies are prerequisite. These procedures are intended to supplement, not to replace, the usual forms of investigation.

What especially commends these ancillary diagnostic techniques are their simplicity and their relative innocuousness. When they work, they enable us to avoid being pressed into giving our therapy in the dark, a situation which none of us particularly relishes. Without a proper diagnosis, we find ourselves, now and again, employing measures which prove useless and sometimes even harmful because of the serious side-effects of some of the agents we employ today.

In Table I are listed some diagnostic procedures now in fairly common use. Most of them are aimed at establishing a tissue diagnosis by biopsy or by cytologic studies. Some depend upon the patient's reactivity to a specific intradermal test. Others are biochemical studies directed at uncovering certain abnormalities associated with some chronic lung diseases. I have consciously omitted one extremely important area of investigation, namely, lung function studies. Lung function studies have become indispensable to our understanding

From the Thoracic Disease Service of the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

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of many pulmonary conditions but their purpose is not purely diagnostic and, hence, they are not really germane to the present topic.

A number of histopathological techniques deserve pride of place because I deem them preeminent in the diagnosis of many puzzling lung conditions.

TABLE I
Ancillary Techniques in Investigation of Chronic Lung Disease

Technique	Diseases Where Applicable
1. Open lung biopsy (Klassen) local anesthesia	Diffuse lung diseases; Sarcoidosis, Hamman-Rich syndrome, honeycomb lung, histiocytoses, pneumoconiosis, beryllium disease.
2. Open thoracotomy general anesthesia	Localized nodule; Tuberculoma, histoplasma, benign or malignant neoplasm
3. Scalene node biopsy (Daniels) local anesthesia	Diffuse or localized lung disease with mediastinal adenopathy; Sarcoidosis, carcinoma, tuberculosis, Hodgkin's disease.
4. Pleural needle biopsy (open biopsy if needle biopsy fails) local anesthesia	Tuberculous or carcinomatous pleural effusion or pleural "scallopings."
5. Paracarinal biopsy via bronchoscopy (Rabin)	Carcinoma of major bronchus; assessing whether operable
6. Random biopsies of muscle, nasal mucosa, region of old scars (Löfgren)	Sarcoidosis
7. Cytologic examination; sputum, bronchial washings, pleural fluid	Malignancy of lung and pleura
8. Intradermal tests; tuberculin, histoplasmin, coccidioidin, blastomycin (Read at 48-72 hours) Kveim, lepromin and beryllium patch test (Read at 4 weeks with biopsy of test site)	Tuberculosis and fungal diseases. Sarcoidosis, tuberculoid leprosy, beryllium disease
9. Biochemical studies: blood, urine, sweat Hypercalcemia, hypercalciuria Hyperglobulinemia Hypogammaglobulinemia Elevated Na ⁺ , Cl ⁻ in sweat, pancreatic enzyme deficiency Elevated lactic dehydrogenase Elevated blood serotonin and 5-HIAA urine levels	Sarcoidosis, beryllium disease, neoplasms Sarcoidosis, Hamman-Rich syndrome Repeated bacterial pneumonias Cystic fibrosis of pancreas, mucoviscidosis Pulmonary infarction Bronchial adenoma (carcinoid) with or without metastasis

LIMITED OPEN LUNG BIOPSY

This is the technique *par excellence* for arriving at a histopathological diagnosis in a host of disseminated lung conditions. The clinical and radiological manifestations of some of these diseases are so much alike that we are unable to make a diagnosis without tissue corroboration. Limited open lung biopsy supplies such corroboration in about eighty per cent of instances. The value of this procedure rests on the fact that in disseminated lung diseases, what is found in a small portion of excised lung tissue is usually more or less representative of what is present in the whole lung. Through this measure we are now gaining insight into the early changes which occur in some of the more mystifying pulmonary diseases, changes which previously could be observed only in their end stages at postmortem examination. Since lung function studies

are now so necessary in our investigations, it has become increasingly urgent that we fashion some correlation between the anatomic abnormalities found in the lung and the physiologic derangements which we are detecting. Limited open lung biopsy is supplying us with much needed histopathological data for this purpose.

Klassen first introduced open lung biopsy in 1949 and used general anesthesia (1). Today some surgeons prefer to do these biopsies under local anesthesia. Even the most dyspneic patient appears to undergo the procedure surprisingly well. Through a short intercostal incision the surgeon grasps a small lappet of lung which is delivered through the incision by applying positive pressure to the face mask. The extruded edge of the lung is clamped and excised; then after placing a few sutures, the surgeon drops the lung back into the pleural cavity. A water-sealed catheter may be left in the pleural cavity for 24 to 48 hours. Complications such as persistent pneumothorax or hemorrhage are uncommon. The only contraindication is the presence of a bleeding tendency.

The piece of lung is subjected to routine and special histopathological studies but may also be submitted for culture and special stains to detect bacteria, fungi or viruses as well as for chemical, spectrographic and x-ray diffraction analyses. Any one of these studies may prove to be diagnostically decisive.

As examples of the usefulness of limited open lung biopsy, I have chosen four disseminated lung conditions in which the technique is particularly applicable;—idiopathic pulmonary fibrosis (Hamman-Rich syndrome), honeycomb lung, sarcoidosis and pneumoconiosis.

Idiopathic Pulmonary Fibrosis (Hamman-Rich Syndrome)

This condition cannot be diagnosed with certainty during life without histological corroboration. It is rather characteristic that patients with this illness may experience severe tachypnea with a relative paucity of chest roentgen findings. The reverse is often true in sarcoidosis and silicosis; extensive pulmonary mottling may be accompanied by surprisingly few or even no respiratory symptoms.

CASE 1. Figure 1 reproduces the chest film of a 48 year old man made when the patient had been already ill with increasing dyspnea for one year. He exhibited clubbing of the digits and there were fine basilar rales as well as an elevated serum globulin level. The arterial oxygen saturation was reduced to 82 per cent at rest. The vital capacity was only 34 per cent of normal but the maximum breathing capacity was fairly well maintained, at 74 per cent of the predicted level. The lung function studies, in short, showed the presence of an alveolar-capillary block pointing to an abnormality in the interstitium of the lungs without significant obstruction of the small bronchi. The patient's film shows some reticular and micronodular shadows at both bases, more pronounced at the right, but for the most part the lung fields appear well aerated.

On lung biopsy the usual cobblestone surface of the visceral pleura was noted. Microscopically, (Fig. 2) the thickening of the alveolar septa is striking. There is considerable infiltration of the stroma with lymphocytes and

plasma cells and there is also some fibrillary scar formation in the septa. Some of the alveoli are lined with low cuboidal epithelium. In spite of some improvement with steroid therapy the patient succumbed after a few months.

Honeycomb Lung

This condition is not a single etiological entity since it is, in actuality, a prototype of the end stages of interstitial fibrosis. Honeycomb lung is en-

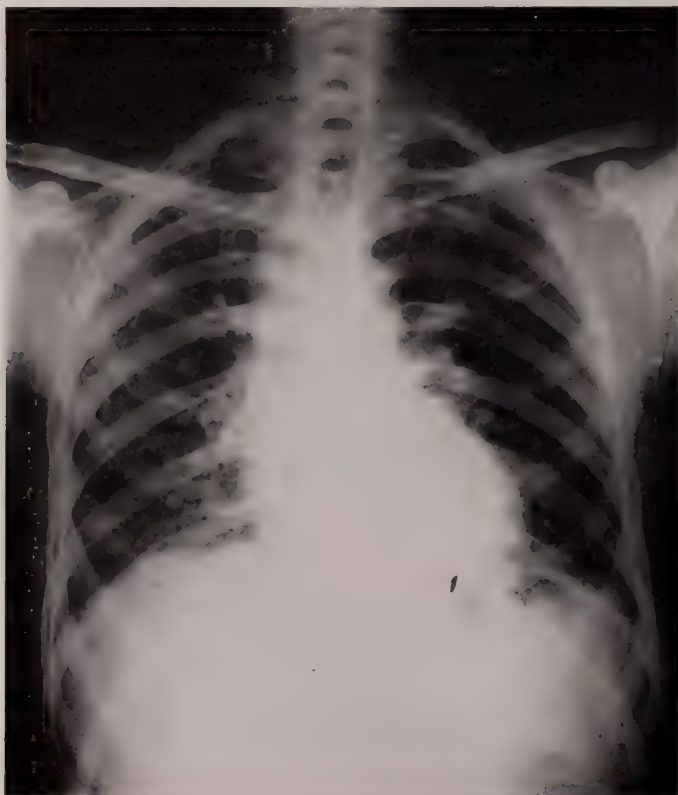


FIG. 1. Case 1. Chest film of patient with Hamman-Rich syndrome showing micronodular shadows at both bases more prominent on the right. In spite of severe tachypnea, lung fields are well aerated.

countered in some patients with Hamman-Rich syndrome, scleroderma, Schüller-Christian disease, tuberous sclerosis and Farmer's lung among others.

CASE 2. Figure 3 represents the chest film of a woman who had had dyspnea for about one year. There are innumerable, rather typical microcysts all of more or less uniform size not exceeding 1 to 2 cm in diameter. For some reason larger cysts or bullae similar to those encountered in emphysema and sarcoidosis are not encountered in "honeycomb lung." Lung biopsy disclosed numerous cystic areas lying within a fibrotic network. Figure 4 shows the wall of a cyst with its cuboidal and columnar epithelium resting on a bed of fibrillary scar tissue infiltrated with a few inflammatory cells. Some exudate is present within the cyst lumen and desquamated epithelial cells lie within an unorganized exudate.

It is not really known how these microcysts are formed. Several hypotheses, none of them very satisfactory, have been advanced to explain their genesis. Some pathologists consider the cysts to be bronchiolectasis resulting simply from traction on terminal bronchi and bronchioles by the fibrosed and obliterated lung tissue. Others regard them as the result of obstruction of terminal bronchial radicles with dilatation resulting from the trapping of air. Still others consider the honeycomb lung as a malformation, a species of hamartoma. Dr. Paul Gross has suggested that the microcysts may result from the abortive

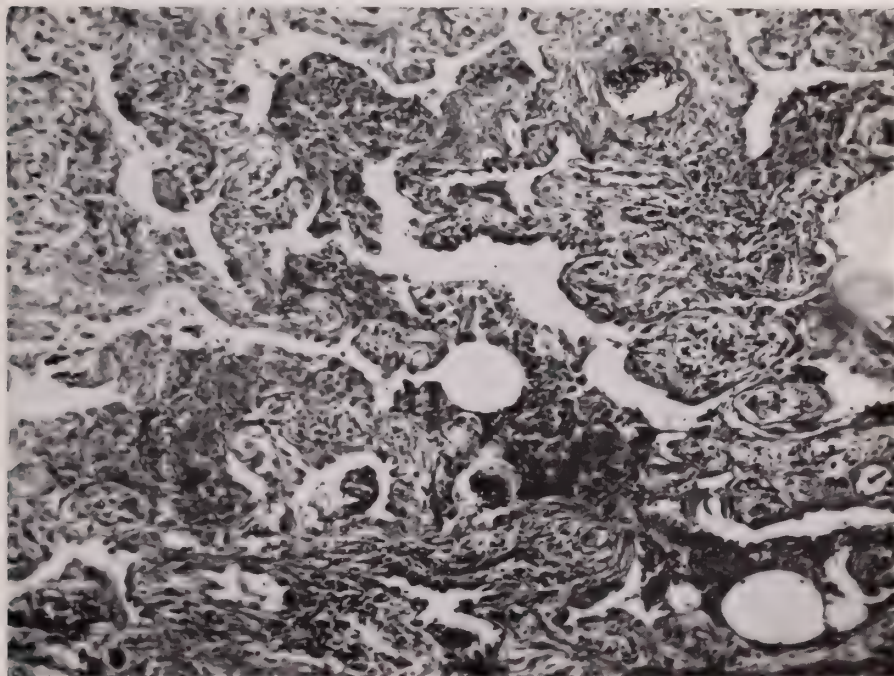


FIG. 2. Case 1. Lung biopsy specimen showing striking fibrillar thickening of alveolar septa which are infiltrated with inflammatory cells. Some of the alveoli are lined with low cuboidal epithelium, a characteristic finding in Hamman-Rich Syndrome.

effort on the part of the lung to regenerate itself, similar to the inappropriate regeneration one sees in bile capillaries after liver damage. Dr. Gross bases his hypothesis on the finding that the walls of the microcysts contain fine uninterrupted strands of young newly formed reticulin fibers which contrast with the thick fragmented reticulin fibers present in the damaged nonecystic portion of the fibrotic lung (2).

Sarcoidosis

Through the next example of the applicability of open lung biopsy, we were able to understand more clearly the basis for a patient's severe dyspnea as well as to employ suitable therapy to combat it.

CASE 3. Figure 5 is a reproduction of a chest film of a 28 year old Negro woman who had complained of severe dyspnea and low grade fever for two months. The lung fields have a veiled and mottled appearance and the root shadows are somewhat accentuated. On closer inspection it became apparent that the shadows in the lung fields were caused by a fine nodular stippling which I sometimes call "Farina" lung. The patient required continuous oxygen therapy and the lung function studies revealed severe impairment of oxygen diffusion across the aveolar membrane. The patient's course was febrile and her condition was deteriorating. A scalene fat pad biopsy proved unilluminating and open lung biopsy was undertaken; for, in spite of a negative tuberculin test, the possibility of miliary tuberculosis



FIG. 3. Case 2. Chest film displaying a "honeycomb lung" with microcysts from base to apex. The cysts measure 1-2 cm in diameter or smaller.

had to be eliminated. Figure 6 shows the epithelioid cell tubercles without caseation which are characteristic but not pathognomonic of granulomas found in sarcoidosis. The myriads of tubercles are quite confluent although some of them are still discrete and are visible in the upper right hand corner of the microphotograph. Corticosteroids promptly controlled the patient's dyspnea and within two weeks she could walk about the wards. The chest film made some months after therapy disclosed almost complete clearing in both lung fields (Fig. 7). Although this young woman became capable of climbing four flights of stairs, a repetition of the lung function studies still show considerable defect in oxygen diffusion in spite of the relatively clear lung fields. It is well known that even complete radiographic resolution in sarcoidosis does not necessarily imply that the granuloma has entirely disappeared from the lungs. This patient has had no relapse in more than one year after discontinuation of steroid therapy, and she works full time.

Pneumoconiosis

In industrial dust diseases such as silicosis, asbestosis and beryllium poisoning, limited open lung biopsy is proving increasingly useful in diagnosis and in illuminating the nature of the pulmonary damage these dusts cause. In asbestosis, Bader, Bader and Selikoff have recently shown that this industrial

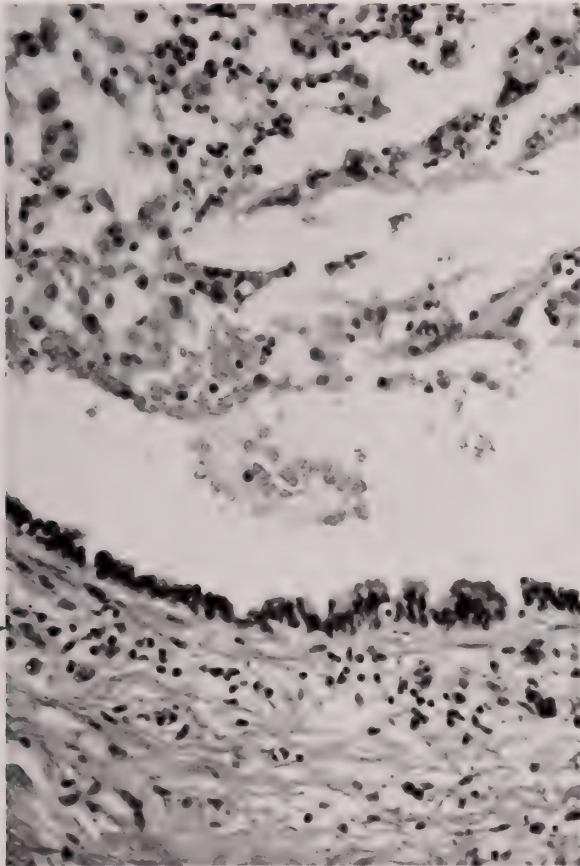


FIG. 4. Case 2. Lung biopsy from a "honeycomb lung" showing the fibrous wall of a microcyst lined by cuboidal and columnar epithelium. The lumen of the cyst contains an exudate with desquamated epithelial cells and some inflammatory cells within it.

dust may cause an alveolar-capillary block syndrome (3). These authors made correlations between the results of lung function studies and the radiographic appearance of the lungs. In some instances open lung biopsy enabled them to study the histopathological alterations underlying the functional defects.

An ingenious method for the study of pulmonary tissue sections in pneumoconiosis has been described recently by Dr. Paul Gross (2). After the pulmonary tissue has been stained by Van Gieson's method it is photographed and then incinerated at 600°C for one hour, charring the lung tissue and leaving the mineral ash behind. A dark field photograph is then made to disclose the

foreign material and this is superimposed on the photograph made initially to give a composite picture. The black mineral deposits stand out well against the stained tissue and by this method Dr. Gross has been able to establish clearly that in silicosis the particles are located in the active peripheral cellular zone and not in the center of the collagen scar. He has also been able to demonstrate that the foreign particles are loosely held in the tissues and that



FIG. 5. Case 3. Chest film of patient with alveolar-capillary block resulting from disseminated pulmonary sarcoidosis. Both lung fields have a veiled appearance but close inspection reveals tiny stippling throughout. The hilar nodes are symmetrically enlarged.

they can migrate to uninvolved portions of the lung when pulmonary edema or pulmonary inflammation supervenes.

OPEN THORACTOMY

A second more familiar diagnostic procedure is exploratory thoractomy under general anesthesia. Mass chest roentgen surveys often disclose solitary nodules in the periphery of the lung among asymptomatic patients. When no substantial amount of calcium can be demonstrated by tomography, it may be very difficult to differentiate an early lung carcinoma from a granuloma or

a hamartoma. Recently, the Gomori methenamine-silver tissue stain has enabled pathologists to identify fungi, mainly *Histoplasma capsulatum* and *Coccidioides immitis*, in granulomas in about 75 per cent of instances (4). By similar methods, fungi have also been identified within broncholiths removed bronchoscopically (5). The stones which represent calcified lymph nodes eroding through the bronchial wall and causing inflammatory strictures usually stem from an obsolete tuberculous infection. In the midwestern United States, where histoplasmosis is a more common cause of mediastinal lymph node calci-



FIG. 6. Case 3. Lung biopsy specimen showing confluent noncaseating epithelioid-cell granulomas containing no acid fast bacilli. In upper right, discrete granulomas are present. This picture is compatible with a diagnosis of sarcoidosis. Kveim test was positive.

fication than tuberculosis, the fungi are now being identified within broncholiths as well.

SCALENE NODE BIOPSY

This procedure, also done under local anesthesia, is in general performed when mediastinal node enlargement of unknown cause is under consideration. Scalene fat pad biopsy has become increasingly common in the last five years.

Daniels used this method to determine whether a carcinoma of the lungs had spread into the lymphatics beyond the thorax (6). Simply by removing the scalene fat pad under local anesthesia in the absence of lymph nodes which could be palpated in the supraclavicular fossae, Daniels was able to detect that the tumor had already reached the lymph nodes in the fat pad. This, of course, rendered any surgical approach to the lung carcinoma useless. May I stress that most lymph nodes in the supraclavicular area which become involved with

metastases can usually be palpated and biopsied directly without excising the scalene fat pad.

By far the most rewarding application of scalene node biopsy, as Daniels realized, lies in the diagnosis of early sarcoidosis. Carstensen found the granuloma in 60 per cent of 200 patients in whom the presence of sarcoidosis was



FIG. 7. Case 3. Chest film of same patient as Fig. 5 showing practically complete clearing of pulmonary clouding with steroid therapy. Granulomas undoubtedly still remain (but not radiologically visible) since lung function studies showed that the diffusion defect persisted in part.

strongly suspected (7). Tuberculosis and silicosis may be discovered by this means on occasion when they involve the lymph nodes of the fat pad.

PLEURAL NEEDLE BIOPSY

A diagnostic maneuver of more recent vintage is aspiration biopsy of the parietal pleura with a Vim-Silverman, Cope or Abrams needle, a simple and rather useful technique. If one is faced with an idiopathic pleural exudate, a specific diagnosis can be obtained by this method in more than half the patients (8, 9). Fragments of parietal pleural tissue adequate for histological

diagnosis should be obtainable in more than three of every four attempts. Our own score with the Abrams needle has been quite satisfactory recently. All of some twenty aspiration specimens contained identifiable pleura.

Among young adults, pleural tuberculosis is the most common condition diagnosed by this method.

CASE 4. Figure 8 shows a chest film of a young woman who had been ill for two weeks with right chest pain and fever. The pleural effusion was a lymphocytic exudate and the tuberculin test was positive. A needle biopsy at the time of the chest tap removed a core of tissue which disclosed diffuse epithelioid cell infiltration of the parietal pleura with an area



FIG. 8. Case 4. Chest film of young woman with a lymphocytic effusion of two weeks' duration in the right pleural cavity.

of caseation in the lower right (Fig. 9). Antituberculosis therapy could be begun with confidence without waiting six weeks for the result of the culture of the pleural fluid for acid fast organisms, which, incidentally, often turns out negative, as it did in this instance.

In older patients, carcinomatous invasion of the pleura causes pleural effusion more often than does tuberculosis. But because of the spotty distribution of the neoplastic deposits on the pleura, this condition is not so easily recognized.

CASE 5. Figure 10 shows the chest film of a 60 year old woman with recurrent effusion on the left side. No malignant cells could be identified in the fluid and the endobronchial tumor

in the left upper lobe could not be visualized by bronchoscopy. Tissue obtained through a needle biopsy revealed the parietal pleura to be extensively infiltrated by a carcinoma of undetermined type (Fig. 11).

On the basis of this and similar experiences, it is now our conviction that needle biopsy of the pleura is useful and should become part of the routine chest tap procedure when the etiology of an effusion is not clear. When pleural thickening without fluid is present, the needle biopsy technique is less satisfactory.

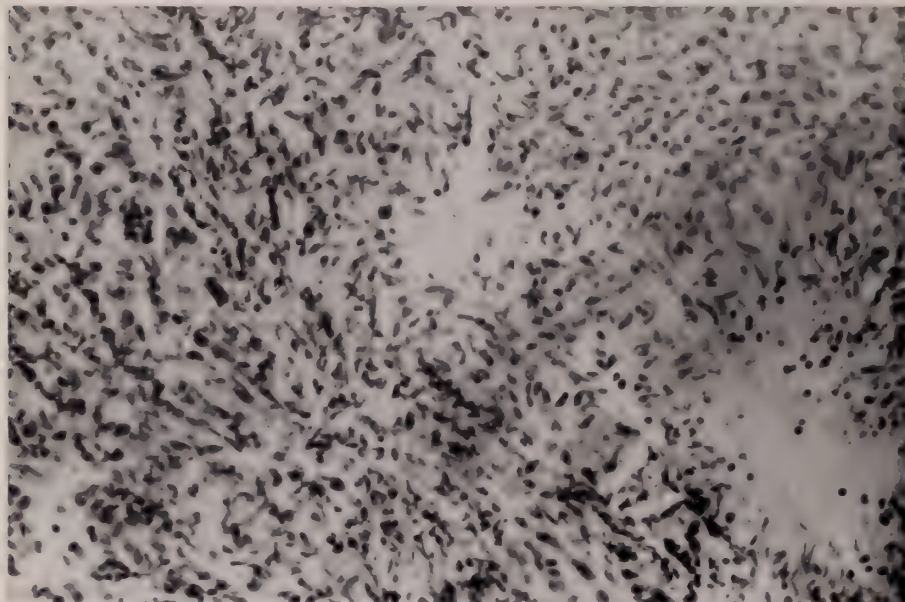


FIG. 9. Case 4. Section of parietal pleura obtained by needle aspiration shows diffuse epithelioid cell infiltration with area of caseation in lower right. No AFB.

PARACARINAL BIOPSY

The paracarinal biopsy technique described by Rabin, Selikoff and Kramer is not primarily a diagnostic procedure (10). Its object is to assess whether a lung carcinoma is operable. It is employed when a bronchogenic carcinoma is visible through a bronchoscope and is at some distance from the carina. A bronchoscopic biopsy of the main bronchus on the side of the carcinoma is performed 1 cm beyond the bifurcation of the trachea. Beneath an apparently normal mucosa in this region, tumor cells may be found in the submucous lymphatics in one of every six cases studied.

Since surgeons are required to leave a bronchial stump of at least 1 cm in length when they perform a pneumonectomy, the presence of carinal spread of tumor contraindicates the operation. Involvement is more common with carcinoma of the right lung than of the left.

CASE 6. Fig. 12 shows the paracarinal biopsy of a patient with a bronchoscopically visible right lower lobe carcinoma. In the submucosa one sees the lymphatics filled with carcinoma cells. Some of the tumor cells are unusually large and possess hyperchromatic nuclei. In this case the patient received radiotherapy rather than surgical treatment.

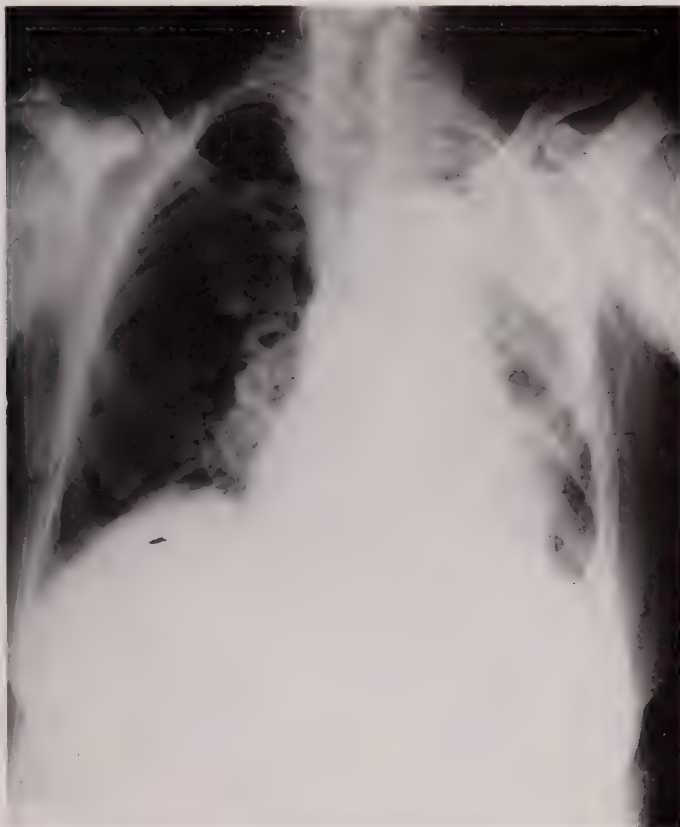


FIG. 10. Case 5. Chest film of patient showing clouding of left upper lobe with a left upper lobe root mass. Some fluid is present at the base of the left pleural cavity. Bronchoscopy had disclosed no visible tumor.

RANDOM BIOPSIES OF MUSCLE, BRONCHIAL AND NASAL MUCOSA, OLD SCARS

The diagnosis of sarcoidosis can sometimes be supported by finding characteristic histological changes in a muscle biopsy (usually deltoid or calf muscle), in biopsy of bronchial and nasal mucosa, or by examination of a nodular deposit in a scar (11).

CYTOLOGIC EXAMINATION: SPUTUM, SECRETIONS BY BRONCHOSCOPY, PLEURAL FLUID

One of the principal obstacles to early diagnosis of a central carcinoma of the lung is the lack of abnormal roentgen findings in the chest until the carcinoma becomes fairly advanced.

Experienced cytologists can now find exfoliated carcinoma cells in sputum and bronchial washings when the bronchial tree still appears to be normal on bronchoscopic and bronchographic examination. Hence, periodic cytologic study of the sputum as well as repeated roentgen examinations have been suggested for earlier detection (12). Cytological examination of pleural fluid is an effective diagnostic technique, and is more sensitive than needle biopsy. Carcinoma cells can be detected in 60 to 70 per cent of patients with pleural metastases.

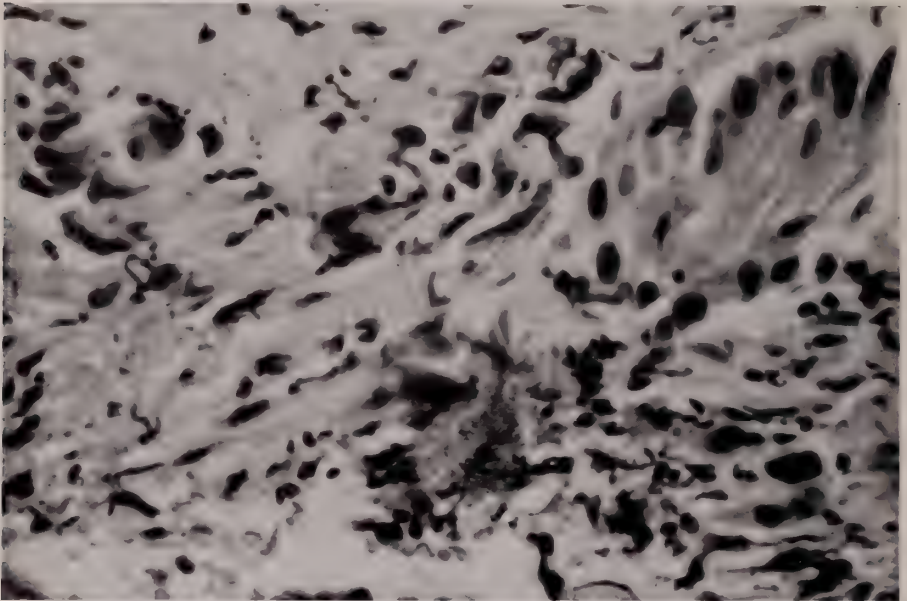


FIG. 11. Case 5. Needle biopsy specimen of parietal pleura showing extensive infiltration with carcinoma of undetermined type.

INTRADERMAL TESTS

The intracutaneous tuberculin and fungal tests are universally used to detect past and present infection with mycobacteria and fungi. In the southern United States dermal reactivity to antigens prepared from atypical mycobacteria are being studied because it has been learned that the same persons who react weakly to purified protein derivative will react strongly to the new antigens. Some of these persons become ill with a pulmonary disease which simulates pulmonary tuberculosis very closely save for the absence of tubercle bacilli in the sputum or gastric contents. The full import of human infection with atypical mycobacteria is yet to be clarified.

The Kveim test is accepted as a basic technique for the diagnosis of active sarcoidosis. More than three of every four patients with active lesions will exhibit a positive reaction. False positive reactions occur in less than two per cent of tests. The test tends to become negative as the sarcoidosis abates (13-15).

The high degree of specificity of the Kveim test has helped us measurably to distinguish the granulomas of sarcoidosis from those caused by tuberculosis, leprosy, beryllium disease and local sarcoid reactions which we encounter more and more often in lymph node draining areas with malignant neoplasms or chronic inflammation. It is hard to imagine how our Sarcoidosis Clinic could function if we did not have available a validated test suspension for its diagnosis.

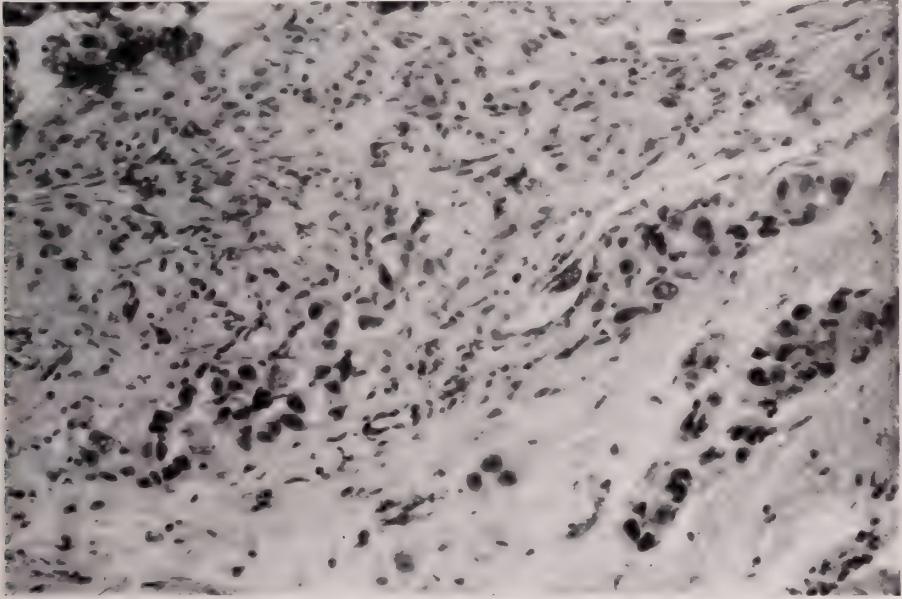


Fig. 12. Case 6. Paracrine biopsy of a patient with a bronchoscopically visible right lower lobe carcinoma. The lymphatics of the submucosa (lower right) are filled with tumor cells possessing large hyperchromatic nuclei.

BIOCHEMICAL ABNORMALITIES

Hypercalcemia, hypercalciuria: Abnormal calcium metabolism is found in sarcoidosis, beryllium disease and occasionally in patients with bronchogenic carcinoma or Hodgkin's disease without apparent osseous involvement. Although increased gastrointestinal absorption of calcium is present, a satisfactory explanation for this phenomenon has not yet been found.

Hyperglobulinemia: This abnormality occurs in about one-third the patients who suffer from sarcoidosis more often in the Hamman-Rich syndrome and the finding has led to speculation that these two disorders may be expressions of an underlying hypersensitive state.

Hypogammaglobulinemia: Patients with hypogammaglobulinemia deal poorly with bacterial infections and are subject to frequent attacks of pneumonia which tend to become chronic. On the other hand, these patients withstand most viral infections.

Elevated lactic dehydrogenase (L.D.): Wroblewski and Gregory recently

subjected lactic dehydrogenase (L.D.) to starch gel electrophoresis and thus detected five separate iso-enzymes (16). They also determined that the level of enzymes designated as L.D. 4 and L.D. 5 was elevated in patients with myocardial infarctions, and the level of enzymes L.D. 2 and L.D. 3 was elevated in patients with pulmonary infarction.

Elevated blood serotonin and 5-HIAA urine levels: The carcinoid syndrome was first described in patients with metastasizing carcinoid tumors of the gastrointestinal tract. This syndrome has also been seen with metastasizing bronchial adenoma (17). Patients with the carcinoid syndrome display typical attacks of flushing, diarrhea, bronchoconstriction, edema and structural abnormalities of the heart. The level of 5-hydroxytryptamine (serotonin) in the blood is usually elevated as is the level of the 5-hydroxyindoleacetic acid in the urine (5-HIAA). Recently two patients with bronchial adenomas exhibited raised levels of both substances with symptoms of the carcinoid syndrome. Surgical removal of the tumors resulted in a prompt fall to normal levels of blood serotonin and urinary 5-HIAA levels (18). The carcinoid syndrome may also occur with oat cell carcinoma.

I realize that I have touched on little not already known. But it seems to me helpful periodically to sum up the state of our knowledge in various segments in the study of pulmonary diseases, even at the risk that such a summary may contain many truisms. The main point which I want to emphasize is that we now have a battery of techniques, of quite respectable size, which we can use for arriving at a precise diagnosis and prognosis in pulmonary disease. If we select these techniques judiciously and use them in proper sequence we will find ourselves at a level desirably close to our optimum and thus we may gain for our patients and ourselves the best that is within reach.

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GASTROJEJUNAL ULCER FOLLOWING GASTRIC RESECTION FOR BENIGN GASTRIC ULCER

ARTHUR H. AUFSES, JR., M.D., AND GERSON J. LESNICK, M.D.

New York, N. Y.

Anastomotic or jejunal ulceration is so rare following partial gastrectomy for benign gastric ulcer that some surgeons have denied its existence. By contrast there is a five to ten per cent incidence of marginal ulceration occurring in patients with duodenal ulcer subjected to gastrectomy alone.

The rarity of marginal ulcer after gastric resection for gastric ulcer may be explained by the high incidence of postoperative achlorhydria induced by the operative procedure in these patients (1). However, in the patient with gastric ulcer and with coexistent duodenal ulcer, a high incidence of marginal ulceration may be expected. Marginal ulceration may also occur if the operative procedure has been inadequate, *i.e.* antral mucosa remains to stimulate gastric secretion (2).

Recently, two patients who had a marginal ulcer following adequate gastric resection for benign gastric ulcer were treated at The Mount Sinai Hospital. These cases are of interest because the diagnosis was unequivocally established. The preoperative roentgen films showed a normal duodenal bulb. The gastrectomies were adequate. Each of the operative specimens demonstrated a gastric ulcer and included a rim of normal duodenal wall. Nevertheless, jejunal ulceration developed and necessitated reoperation. In one case the recurrent ulcer was perforated.

CASE REPORTS

Case 1

L.J., a 70 year old white male, was admitted to The Mount Sinai Hospital for the first time on July 6, 1955, with the chief complaint of abdominal pain and weight loss of ten weeks' duration. The pain, primarily upper abdominal, was not clearly related to food intake and was intermittently relieved by alkali. There was occasional vomiting and a ten pound weight loss.

Physical examination revealed a thin white male with evidence of recent weight loss. The temperature was 99.8°; the blood pressure was normal; the pulse was 86 min. and irregular. The heart was enlarged; there was an irregular rhythm and a moderate systolic murmur at the apex. The lungs were hyperresonant with decreased breath sounds. There was generalized minimal abdominal tenderness.

Complete blood count and urinalysis were normal. Stool guaiac examination was negative. The electrocardiogram was unremarkable except for auricular fibrillation. The gastric analysis after histamine showed a free acid of 110 mEq/L and a total acid of 140 mEq/L. Roentgen examination of the gallbladder showed a functioning gallbladder containing multiple faceted stones. Gastrointestinal series revealed a persistent patch of barium in the antrum about four centimeters proximal to the pylorus. The roentgen appearance was that of a benign gastric ulcer. The duodenum was normal (Figs. 1 and 2).

The patient was placed on a rigid ulcer regimen. Repeat roentgen studies after 3½ weeks

From the Department of Surgery, The Mount Sinai Hospital, New York, N.Y.

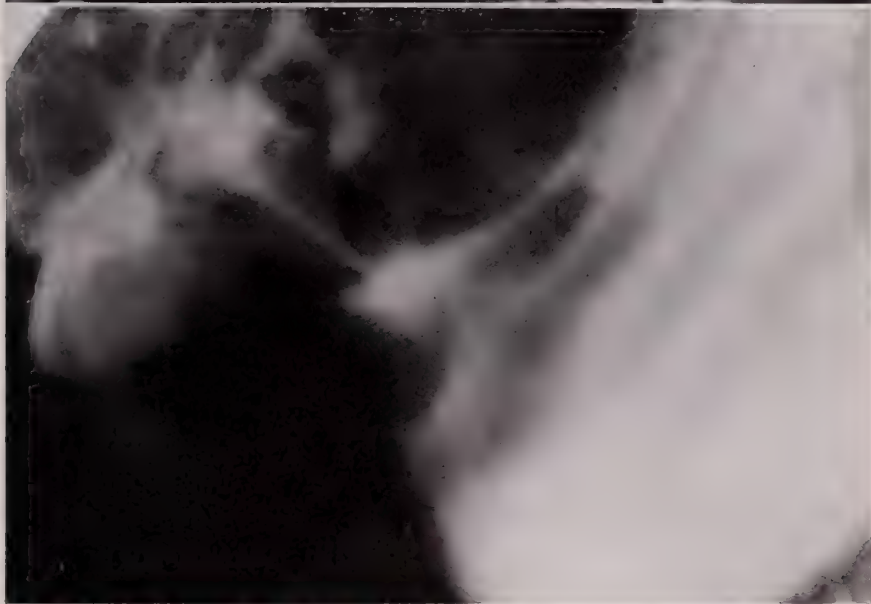


FIG. 1. Case 1. X-ray showing the deformity and ulcer in the antral area and the normal duodenal bulb.

FIG. 2. Case 1. Close-up view of the gastric ulcer.

of therapy showed complete healing of the ulcer. The patient was discharged to continue his ulcer regimen.

He did well until three days prior to the second admission when abdominal pain recurred, becoming more severe and generalized on November 25, 1955, at which time he was re-

admitted. He was acutely ill. The abdomen was rigid, and there was generalized direct and rebound tenderness. There were no peristaltic sounds, and there was absence of normal liver dullness.

The patient was taken to the operating room where laparotomy disclosed a perforated gastric ulcer $2\frac{1}{2}$ cm proximal to the pylorus. The duodenum was normal. A primary gastrectomy was performed. Gastrointestinal continuity was reestablished with an antecolic Hofmeister gastrojejunostomy. The postoperative course was uneventful and he was discharged



FIG. 3. Case 1. X-ray demonstrating a jejunal ulcer opposite the gastroenterostomy stoma.

on the 14th postoperative day. The resected specimen showed a chronic peptic ulcer of the stomach with perforation.

Following gastrectomy the patient did well for two years; then he had recurrence of abdominal pain. In December 1957 he was again admitted to the hospital for study. Physical examination was essentially as before. The wound was well healed. A gastric analysis showed the presence of a small amount of free hydrochloric acid. Gastrointestinal roentgenograms revealed slight thickening of the mucosal folds of the jejunum in the immediate vicinity of the anastomosis, but no recurrent ulceration was noted. The gallstones were again visualized. He responded to hospital management with disappearance of pain.

The patient then did well for eleven months, at the end of which time he again required admission for pain. There were no new findings on physical examination. X-rays showed evidence of a marginal ulcer in the jejunum opposite the gastroenterostomy stoma (Fig. 3).

On December 18, 1958 he was operated upon for the second time. A marginal ulcer was

found (Fig. 4). The gastrojejunostomy was taken down, and additional gastric resection performed. Jejunojejunostomy and gastrojejunostomy were accomplished, followed by vagotomy and cholecystectomy. Once again the postoperative course was unremarkable, and he was discharged two weeks after surgery.

He had no further gastrointestinal symptoms until September 1959 when he died following emergency operation for small bowel volvulus. Postmortem examination was not obtained.

Case 2

F.W., a 67 year old white male, was admitted to The Mount Sinai Hospital on February 19, 1959 complaining of abdominal pain. He stated that he had been well until five months prior to admission when he noted the onset of vague epigastric discomfort after meals associated with mild nausea. One month prior to admission there was a period of nine days when his stools were black; otherwise the stools were normal. His pain, which occurred irregularly



Fig. 4. Case 1. Pathological specimen containing the large, deep, punched-out jejunal ulcer.

throughout the day, did not appear to be relieved by food or milk but was alleviated by "Manhattan" cocktails. Two weeks prior to admission, after gastrointestinal x-rays, he was told that he had an ulcer and required hospital admission. Since the onset of the illness, there had been a loss in weight of 26 pounds.

Physical examination showed an obese, florid man who appeared vigorous and younger than his stated age. The blood pressure was 115 systolic, 65 diastolic; the pulse was 85 min; the temperature was 98.6°. There were no significant abnormalities on physical examination. The complete blood count and urinalysis were normal. Roentgen examination of the upper gastrointestinal tract revealed a large ulcer crater, irregular in contour, on the lesser curvature of the stomach near the reentrant angle. There was widening of the mucosal folds around the crater. The antrum lacked distensibility. The duodenal bulb was normal (Fig. 5). There was a large diverticulum of the second portion of the duodenum. These changes were interpreted as the result of an irregular ulcer of the stomach having many benign characteristics. The possibility of a neoplastic process, however, was not completely excluded. Gastric analysis showed a free acid of 60 mEq/L.

On February 24, 1959, the patient was explored. There was a large gastric ulcer located on the posterior wall of the stomach near the lesser curvature of the antrum. Induration of the gastric wall extended for a diameter of 8 to 9 centimeters. The ulcer crater measured three centimeters. The ulcer had perforated all coats of the stomach and had penetrated into the root of the mesocolon near the origin of the middle colic vessels. There were no abnormally enlarged lymph nodes and there was no evidence of metastatic disease.

The stomach was subtotally resected with a one centimeter rim of duodenum and with the greater omentum. The duodenal stump was closed and gastrointestinal continuity restored by an antecolic type of gastrojejunostomy. Drains were placed to the site of the ulcer bed in the transverse mesocolon.

The resected specimen consisted of a segment of stomach measuring 17 cm along the

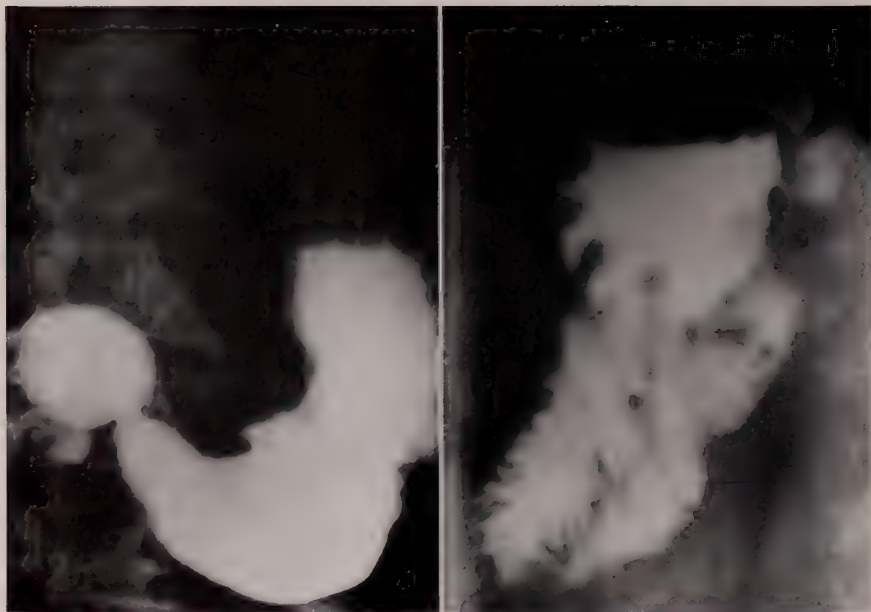


FIG. 5. Case 2. X-ray demonstrating the large gastric ulcer on the lesser curvature and the normal duodenal bulb.

FIG. 6. Case 2. Postoperative x-ray showing the small residual gastric pouch.

greater curvature, 9 cm along the lesser curvature, and 8 cm along the proximal line of resection. There was an attached rim of normal duodenum. In the center of the lesser curvature was a deep ulcer measuring 2 by 3 cm with an indurated margin. Histologic examination confirmed the diagnosis of a benign peptic ulcer of the stomach.

Following operation, the patient did well for four days. He then had a pulmonary infarction with tachycardia, tachypnea, and hypotension. He recovered from this episode and was given anticoagulant therapy to prevent further thrombosis. After one dose of sodium warfarin his prothrombin time rose over a period of six days to hemorrhagic levels. This was followed by a massive gastrointestinal hemorrhage which required transfusion of 3500 cc of whole blood and packed red blood cells as well as intravenous vitamin K.

The patient was discharged, essentially asymptomatic, on April 6, 1959, 41 days after operation. He did well and returned to a full diet including his precibal cocktails.

On September 9, 1960 he was admitted to another hospital because of the passage of a tarry stool and syncope. He had, also, vomited blood stained material. On admission to the hospital he was pale. Blood pressure was 110 systolic, 80 diastolic; the pulse rate was 108 min.

There was a well-healed epigastric scar. Rectal examination yielded stool which gave a positive reaction for blood.

The hemoglobin was 10 Gm%; the hematocrit 31%; R's 39 Gm%; and the prothrombin time was normal, as was the bleeding time. Gastrointestinal roentgenograms showed the status following a high subtotal gastrectomy; the stomach appeared normal (Fig. 6). There was no evidence of ulceration.

He was treated conservatively. Blood was demonstrated in the stomach by passage of a nasogastric tube. He was given blood transfusions and received a total of thirteen pints of blood in five days. Thereafter, there was no bleeding. However, bilateral bronchopneumonia developed, as well as congestive heart failure which responded to antibiotics and digitalis. He was discharged fourteen days after admission for further convalescence.

After discharge he felt well and returned to his usual activities until April 7, 1961. On this date, during lunch he noted sudden abdominal discomfort associated with a feeling of weakness and sweating. He could not continue eating. Abdominal pain persisted until admission to the hospital three hours later.

Examination revealed an acutely ill male lying quietly in bed. The temperature was 98.6; the blood pressure was normal; the pulse 110/min. There was generalized abdominal tenderness and muscle spasm, most pronounced in the left lower quadrant. Scout film of the abdomen showed a few patches of gas in the small and large intestine. There was no free air discernible in the peritoneal cavity.

Laparotomy was performed, and a moderate amount of purulent exudate was noted. The peritonitis was due to a perforation of an ulcer of the jejunum, located at the mesenteric margin of the anterior wall of the jejunal segment opposite the gastroenteric stoma of the previous gastrectomy. The ulcer was two centimeters in diameter with an indurated rim. There were no other abnormalities noted in either the jejunum or the gastric pouch. The duodenal stump was normal. The pancreas was inspected and palpated, and no tumor was observed.

The lesion was treated by resecting the involved segment of jejunum with a two centimeter rim of stomach. Intestinal continuity was restored by a jejunojejunostomy and a new gastrojejunostomy just distal to the jejunojejunostomy. An infradiaphragmatic vagotomy was then performed, and segments were excised from two large vagus nerve trunks. The resected specimen showed a large, perforated, benign peptic ulcer of the jejunum located opposite the gastroenteric stoma.

His recovery after this operation was uneventful except for moderate diarrhea for fourteen days. He was discharged from the hospital three weeks after operation.

DISCUSSION

Gastric resection has been eminently successful in the management of benign ulcer of the stomach. There are usually fewer digestive symptoms in the post-operative period than there are following surgery for duodenal ulcer, and, marginal ulceration is extremely rare. Marshall has stated that, "no proven recurrent ulcers developed after resection for gastric ulcer in 411 cases" (3).

Balint *et al.* studied 160 patients with anastomotic ulcer; only two of these followed surgery for gastric ulcer (4). Beal reviewed 204 cases of marginal ulceration treated at the New York Hospital (5). In 157 patients the original pathology was known. One hundred and forty-nine patients had had surgery for duodenal ulcer; only eight had been operated upon for gastric ulcer. Priestley and Gibson note that gastric ulcer was the original lesion in only 1.4 per cent of cases of marginal ulceration treated at the Mayo Clinic (6).

The actual statistical incidence of marginal ulcer following resection for gas-

tric ulcer is probably lower than these figures would indicate since these papers do not differentiate the patients with gastric ulcer treated by resection from those treated by gastroenterostomy. In these papers here has been no attempt to correlate the development of marginal ulceration with the level of acid secretion.

In addition, in most studies, patients with gastric and duodenal ulcer have been grouped together. Cornell and Druckerman have pointed out that this practice is invalid since physiologically the two lesions are different, and their response to gastric resection is not the same (1).

Ransom reviewed 188 patients with gastric ulcer subjected to resection (2). In this group, marginal ulceration subsequently developed in four patients. Of note is the fact that three of these patients had had a Finsterer antral exclusion procedure, and, in at least two of them, antral mucosa was known to be left *in situ*. Brown and Hoerr reported a patient with gastric ulcer who underwent an 80 per cent gastric resection (7). Gastrointestinal continuity was re-established by gastroduodenostomy. This patient had a recurrent ulcer in the duodenum which responded to nonoperative therapy.

The development of marginal ulceration is dependent upon acid production in the residual gastric pouch. Winkelstein has commented: "no postoperative free acidity, no recurrent ulcer" (8).

Levin and his co-workers have shown that patients with gastric ulcer have a nocturnal gastric secretion of about the same volume as normal controls, but that the hydrochloric acid content is lower than normal (9). This is in marked contrast to the hypersecretion of duodenal ulcer patients. Of the 105 cases of benign gastric ulcer studied by Marshall and Welch, 65 per cent had acid values that were normal or lower than normal (10). An additional 13 per cent of the entire group were anacid.

With these findings in mind one can expect gastric resection to produce anacidity in a higher percentage of patients with gastric ulcer than in patients with duodenal ulcer. Cornell and Druckerman have shown that, whereas 90 per cent of patients with gastric ulcer subjected to resection will manifest a postoperative achlorhydria, only 55 per cent of patients with duodenal ulcer will be anacid after gastrectomy (1). They also point out that the marginal ulcers occurring in the duodenal ulcer patients were in those patients in whom free acid could be found in the postoperative period.

There is, therefore, a lower incidence of recurrent ulceration in the gastric ulcer patient as compared to that in the patient with ulcer disease of the duodenum. Because of this, vagotomy has not often been recommended as an adjuvant to resection in the surgical management of gastric ulcer.

The very high acid values in Case 1 would today suggest the possible presence of the Zollinger-Ellison syndrome (11, 12). The result of a single histamine gastric analysis, however, is not sufficient evidence upon which to base such a diagnosis. We believe, that in addition to the standard histamine gastric analysis, all patients with ulcer disease should have confirmatory proof of excessive gastric secretory capacity in the form of studies on nocturnal gastric secretion

and response to maximal histamine stimulation. In Case 1 a pancreatic tumor was not looked for at any of the operative procedures and autopsy was not performed. In Case 2 the pancreas was examined and no tumor found.

The two cases reported here suggest that the surgeon should consider adding vagus section to gastric resection in patients with gastric ulcer when the pre-operative investigation reveals high gastric secretory capacity. It would appear that these cases represent variants of duodenal ulcer disease and should therefore have the additional protection of vagotomy to prevent recurrent ulceration. In addition, the surgeon should be on the alert for the presence of a pancreatic neoplasm in these cases. It must be pointed out, however, that examination of the pancreas can be most difficult and will require mobilization of the duodenum in addition to the body and tail of the pancreas. Even then these tumors may be missed at surgery.

Although rare complications such as these should not make us revise our basic concepts, they nevertheless indicate a need for the reappraisal of surgical therapy in gastric ulcer. Awareness of the possibility of gastrojejunal ulceration following gastrectomy for benign gastric ulcer will undoubtedly disclose additional instances of this complication.

SUMMARY

1. Two cases of gastrojejunal ulcer following gastrectomy for benign gastric ulcer are reported, and the reasons for the rarity of this complication are discussed.

2. Vagotomy may be indicated as an adjuvant to resection in the surgical treatment of some gastric ulcers.

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SERUM ELECTROPHORESIS ON POLYACRYLAMIDE GEL IN LIVER DISEASE*

FENTON SCHAFFNER, M.D., EDWARD J. SINGER, PH.D., DONALD D.
ANTHONY, M.D., AND FRANK J. POPPER

New York, N. Y.

Alterations of serum proteins with the aid of various flocculation and turbidity reactions have been used more or less empirically for the diagnosis of liver diseases, particularly cirrhosis (1). More recently the alteration of the large serum protein fraction, gamma globulin, has attracted interest because of its origin from mesenchymal cells (plasma cells) and the activation of the hepatic mesenchyme in cirrhosis. Free and zone electrophoresis indicated the subdivision of gamma globulin into two fractions (2, 3). Starch electrophoresis as described by Smithies permitted further subdivision (4). When electrophoresis with polyacrylamide gels was recently described (5, 6), it appeared promising from a diagnostic standpoint to survey the use of this rapid technique in patients with liver diseases, particularly since many of the bands of protein demonstrated had been identified under normal circumstances (7).

MATERIALS AND METHODS

Sera from 46 patients (14 with viral hepatitis, 14 with cirrhosis, 5 with obstructive jaundice, and 13 with miscellaneous conditions, mainly or in part involving the liver, such as sarcoidosis, schistosomiasis, Hodgkin's disease and Wilson's disease) and 5 normal controls were collected. Total protein and turbidimetric gamma globulin were determined in all sera and the cephalin flocculation test was run on most specimens (8). The sera were subjected to electrophoresis in polyacrylamide gel with samples run in triplicate. Runs were usually repeated so that each specimen was studied six times or more. For preparation of the gel, (6) equal volumes of four solutions were mixed in the following sequence: 1) 30% acrylamide (Borden Chemical Company, Monomer-Polymer Labs) and 0.8% methylene-bis-acrylamide in distilled water; 2) 0.16 ml beta-dimethylaminopropionitrile (Matheson, Coleman and Bell) freshly diluted to 10 ml with distilled water; 3) 0.03% potassium ferricyanide (reagent grade); 4) 2.4% ammonium persulphate (reagent grade) prepared at 3 week intervals and diluted 1:5 prior to use. To reduce catalyst decomposition by oxygen, the final solution was degassed for two minutes on a vacuum line. Glass tubes, 0.5 cm in diameter and 8 cm long, were stoppered at one end; the tubes were three-fourths filled with the mixture, taking care to prevent formation of

From the Departments of Medicine and Pathology, The Mount Sinai Hospital, New York, N. Y.

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bubbles, and maintained in a vertical position at 37°C. for 30 minutes by which time polymerization was completed. The electrophoresis apparatus consisted of two plastic chambers positioned one above the other (Fig. 1). The gel containing tubes were attached at their upper end to extensions of the upper chamber while the lower ends were suspended in the fluid of the lower chamber. Sodium glycine buffer (0.5 M at pH 8.7, diluted 10-fold prior to use) was placed in each chamber. Serum samples, diluted 3-fold, were layered on top of the gel in a final volume of approximately 15 lambda undiluted serum). Several runs were made with 2, 4 and 8-fold further dilution of this mixture. The power supply was adjusted to deliver 3 to 5 milliamperes of current (or 120 volts) per tube. Specimens were run 25 minutes during which time the albumin fraction migrated between 2.5 to 3 cm. Following completion of electrophoresis, the gel

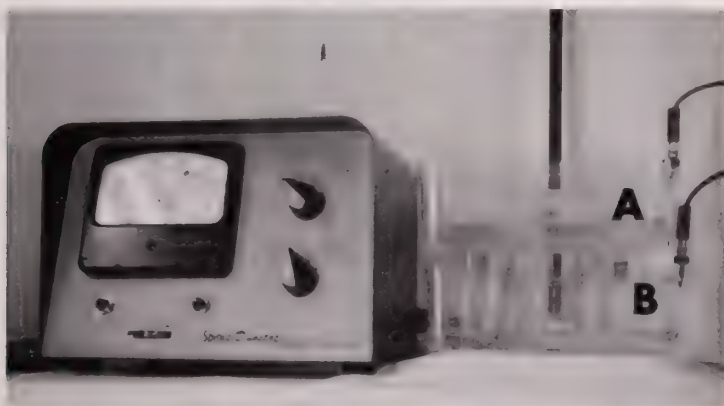


Fig. 1. Electrophoresis apparatus with power supply on left and upper chamber (A) connected to lower chamber (B) by gel-containing tubes.

was removed from its glass casing by rimming it with a metal stylus lubricated with water. The cylinders of gel were then placed in a fixative staining solution consisting of 7 per cent acetic acid saturated with amido schwarz for a period of 45 minutes. The excess dye was decanted, and unbound dye was removed by electrophoresis in 7 per cent acetic acid and the cylinders were stored in this fixative.

Sera from two normal persons were rerun after addition of 20 mg ml of commercially available normal human serum gamma globulin obtained by cold ethanol precipitation. Preparations of the gamma globulin were also run alone.

All cylinders were read under a bright white light with a white background and were photographed in black and white using transmitted light.

Fractions were identified by comparison with starch gel patterns. Utilizing a 5 per cent monomer concentration of polyacrylamide, a pore size similar to that of the starch gel is obtained. Under these conditions distribution of proteins is similar with one exception, *i.e.* most or all of the gamma globulin fraction migrates towards the anode in polyacrylamide gel whereas in the starch

gel migration of this fraction is towards the cathode (6). Reasons for this difference are not completely understood.

In the interpretation of results, genetic variation was recognized and an attempt to select patterns of similar haptoglobin distribution was made where possible for comparison of normal and pathological sera although haptoglobin typing was not done.

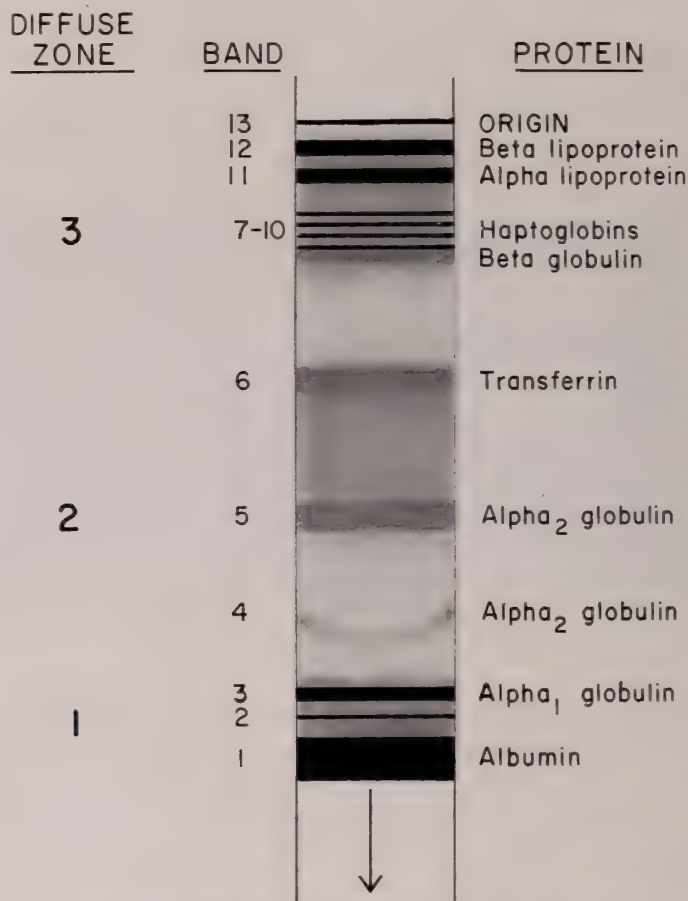


FIG. 2. Diagram of zones and bands seen on electrophoresis with arbitrary designations used for descriptive purposes and protein fractions identified.

Nomenclature used is based upon that of Smithies (4). Reference to bands and zones is arbitrary and is used as a matter of convenience; it is not intended to extend pre-existing systems of classification.

RESULTS

Using this technique sharp bands and broad zones of protein were produced, the latter being characterized by homogeneity not resolved by greater dilution of the specimen. In normal sera the proteins were separated into at least 13 bands and 3 diffuse zones. The most rapidly moving protein was the largest

sharp band and it had the same mobility as purified human serum albumin. Under the conditions used, no clear cut pre-albumin could be seen. Behind this first band was a diffuse zone (Zone 1) in which at least one thin sharp band (Band 2) and a heavier sharp band (Band 3) were apparent. These were alpha globulins. This was followed by a clear zone which sometimes contained a faint and indistinct band of alpha₂ globulin (Band 4) close to the previous one. It was often crescent shaped in contrast to the other bands which were always flat. In the midzone another diffuse and somewhat faint diffuse zone was present (Zone 2). At the beginning and end of this zone, two diffuse and variably stain-

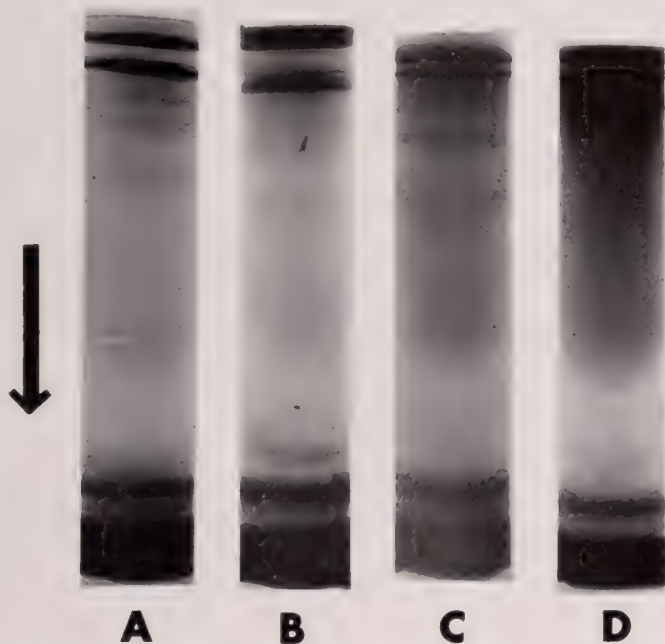


FIG. 3. Serum in cylinders of gel stained with amido schwarz. A, hypogammaglobulinemia, B, acute viral hepatitis, C, stone obstructing common bile duct, and D, active postnecrotic cirrhosis with high serum gamma globulin.

ing bands were seen (Band 5 was alpha₂ globulin and Band 6 was transferrin, a beta globulin). Behind this was another diffuse zone (Zone 3) which contained several bands. Furthest from the origin in this zone were a group of usually 4 (but as many as 5 and as few as 1) sharp fine bands of haptoglobins (Bands 7-10). Band 7 was often broader than the others and supposedly has a beta globulin fraction in it. The haptoglobins were followed by a pair of heavy sharp bands (Bands 11 and 12). Band 11 was probably lipoprotein; Band 12 was variably found and is of uncertain origin. It is known that with aged serum it may be a derivative of Band 11; (6) its occurrence in fresh serum, however, may be from an as yet unidentified fraction. In another series of cases examined by this technique and not herein included, it was found with greater frequency in sera from patients with lupus erythematosus. Finally, a fainter sharp Band 13 at the origin represented material which did not migrate.

Electrophoresis of gamma globulin alone or after it was added to normal serum produced an increase in intensity of diffuse Zone 3 but did not yield any sharp bands. In one patient with mild acquired hypogammaglobulinemia, the gamma globulin zone was very faint.

In cirrhosis the number of bands was decreased and the gamma globulin zone was increased in size and intensity and seemed to blend into Zone 2. The albumin band was thinner than normal. Alpha₁ globulin bands appeared normal. Band 4 (alpha₂ globulin) was faint or missing. Bands 5 and 6 (alpha₂ globulin and transferrin) became lost in the haziness of Zone 2 and the haptoglobin bands were either reduced in intensity, not clearly discernible from background, or entirely absent. The lipoprotein bands were slightly less heavy and Band 13 was variable. The increase in the gamma globulin containing Zone 3, decrease in number and sharpness of haptoglobin bands, and increase in Zone 2 with diffuseness of the alpha₂ globulin and transferrin bands produced a picture seen only in active cirrhosis with serum gamma globulin levels above 1.8 Gm% and cephalin flocculation 3+ or 4+. This pattern was not altered by greater dilution of the serum sample. When serum gamma globulin was less than this, the pattern was either completely normal or Zone 2 was increased slightly with diffuseness of the alpha₂ globulin and transferrin bands.

In acute viral hepatitis the haptoglobin bands were reduced or indistinct in 12 of 14 cases but neither Zone 2 nor 3 was increased greatly in density so that some bands were still discernible. The faster alpha₂ globulin band was diffuse in three cases and missing in two.

In extrahepatic biliary obstruction the patterns were similar to those in viral hepatitis except that fast alpha₂ globulin was diffuse or missing in 4 of 5 cases. In various granulomatous hepatic diseases and nonhepatic chronic diseases, alpha₂ globulin (Band 5) was diffuse in 9 of 13 cases and haptoglobins were reduced in intensity in 6 of 13 cases. Zones 2 and 3 were not diffusely increased as in cirrhosis.

DISCUSSION

The separation of protein by disc electrophoresis using polyacrylamide gel is a simple and rapid technique applicable to screening or surveys. It is being refined by standardization of gel preparation and by introduction of optical devices permitting quantitation of the fractions separated. However, use of this technique for the subdivision of gamma globulin under normal circumstances and in liver disease has thus far not been successful. Furthermore, qualitative results of protein separation could not be correlated with results of commonly used tests such as cephalin flocculation. In cirrhosis the alteration noted is not that the resolution of gamma globulin into recognizable components but rather a smudging of many of the bands of other proteins. This may be the result of quantitative increase of gamma globulin obscuring the bands or of qualitative changes among the protein fractions particularly in their ratio to one another occurring in this disease. Failure of further serum dilutions to influence the cirrhotic pattern suggests the latter.

In cirrhosis more so than in hepatitis, changes of serum proteins other than

gamma globulin can be recognized with this method, namely, increase of beta globulins and decrease of haptoglobins and alpha globulins. Together with the diffuse increase in gamma globulin, these produce a characteristic picture of the serum protein with polyacrylamide electrophoresis. The sharp bands seen in normal serum are replaced by a broad indistinct zone beginning near the origin and extending for about two-thirds of the electrophoretic pathway. As an observation independent of its basic significance, this may be useful in confirming the presence and activity of cirrhosis by a rapid electrophoretic method, in its implications almost comparable to a flocculation test.

SUMMARY

Sera from 46 patients, mainly with liver diseases, were subjected to electrophoresis on polyacrylamide gel. A number of bands of protein were visualized including albumin, several bands each of alpha and beta globulins and haptoglobins. Gamma globulin was not resolved into any discrete bands under normal circumstances (even after adding gamma globulin) or in cirrhosis but was a diffuse slow moving zone in which bands of other proteins could be seen. In hepatitis, obstructive jaundice and various chronic diseases, some involving the liver and others not, haptoglobins were frequently reduced and beta globulins were altered but no characteristic pattern could be distinguished. In active cirrhosis when serum gamma globulin levels are above 1.8 Gm% and cephalin flocculation is 3 or 4 plus the increase in gamma globulins and beta globulins and decrease in alpha globulins and haptoglobins produced a typical pattern that may have some diagnostic value.

ACKNOWLEDGMENT

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COMBINED GASTRIC AND DUODENAL ULCERS*

ALVIN M. GELB, M.D., AND ADRIAN BECKER, M.D.

New York, N. Y.

The combination of gastric and duodenal ulcer in the same patient is not an infrequent circumstance. Although investigations concerning this concurrence have been the basis of several recent reports, lack of agreement exists as to incidence, the role of pyloric obstruction in the etiology of the gastric ulcer, and the existence of hypersecretion of acid. Further, in comparison to simple gastric or duodenal ulcer, information is scant as to the clinical course of these patients. For these reasons it was thought worthwhile to review our experience in this combination of ulcers.

SELECTION OF CASES AND INCIDENCE

The records of all cases of gastric ulcer at The Mount Sinai Hospital from January 1955 through September 1958 were reviewed. Only those cases in which the ulcers were definitely demonstrated by x-ray, at surgery, or on the specimen, either surgical or postmortem, were acceptable; those cases in which the second ulcer appeared only in the history were eliminated from consideration. Also eliminated were those cases in which the gastric ulcer was subsequently proved to be malignant, since it was felt that these were probably malignant from inception and, therefore, were not pertinent to the present study. During this period 315 studied cases of gastric ulcer met the above criteria. Of these, 25 had a duodenal ulcer some time in their life, an incidence of 7.9 per cent.

The charts of all duodenal ulcer patients from the years 1954 through 1959 were also examined. Of this group, using the same criteria for selection, there were 1120 acceptable cases of duodenal ulcer, of whom 36 had had a gastric ulcer in their history, an incidence of 3.2 per cent. There was overlapping of both series so that the total number of proved cases of combined ulceration was 53 cases among 1435 peptic ulcer patients, an incidence of 3.7 per cent. These 53 cases were subjected to detailed analysis.

ANALYSIS OF 53 PROVED CASES

Age: The average age at time of the admission in which the combined ulcer was demonstrable was 58 years. The range was from 27 to 84 years. In 52 patients on whom the information was available, the average age of onset of symptoms was 48 with a range extending from 16 to 84 years of age. The age distribution by decade is presented in Table I, and the duration of symptoms prior to the discovery of the combined ulcer in Table II.

From the Division of Gastroenterology, the Department of Medicine, The Mount Sinai Hospital, New York, N. Y.

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Sex: There were 38 males (72%) and 15 females (28%), a sex ratio of 2.5 males for each female.

Sequence of Appearance: In 23 patients the duodenal ulcer presented first, on the average 10 years, but in two cases as long as 28 years, prior to the appearance of the gastric ulcer. In four the gastric ulcer preceded the duodenal by an average of 7½ years. In nine patients the ulcer symptoms occurred for six months or less prior to the discovery of the combined ulcer on the original x-rays. In 17 patients it was impossible to determine the time sequence either because x-ray prior to admission had revealed an ulcer, site unspecified, or the history extended over many years during which time no attempt at specific diagnosis had been made. Thus, the duodenal ulcer preceded the gastric ulcer in 64 per cent of cases wherein the time sequence was known.

Site of gastric ulcer: In 22 patients (42%) the gastric ulcer was in the

TABLE I
Distribution of Ages on Admission and at Onset of Symptoms

Age	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
Admission		2	4	7	16	15	8	1
Onset of symptoms	1	7	8	9	16	9		1

TABLE II
Duration of Symptoms Prior to Discovery of Combined Ulceration

Duration in Years	0-½	½-1	2-5	6-10	11-20	21-30	31-40	41-50
Number of Patients	10	4	11	9	11	5	1	1

antrum or prepyloric segment; in 26 patients (50%) the ulcer was in the body or cardia. In five patients (9%) there were multiple gastric ulcers, four patients having two gastric ulcers and one patient having three.

Characteristics of duodenal ulcer: In many of the cases a definite crater was not seen in the duodenum on x-ray, but the bulb was described as having constant deformity. Since craters may be present and not demonstrable, it is not possible to be certain in how many cases the ulcers were simultaneously active, nor in how many the duodenum was the site of a scar from previous ulceration. The latter circumstance was frequent in the surgical specimens, although the exact incidence is again unknown since a portion of the bulb, and occasionally the ulcer itself, was not removed because of technical problems at surgery. It was our impression that the location and anatomical features of the duodenal ulcers did not differ from those of uncomplicated duodenal ulcers.

Secretory tests: In 21 patients, 15 male and 6 female, a gastric analysis using 0.5 cc histamine was recorded. The highest value for total and free acid

was tabulated for each patient. For males, the average total acid was 83.7 mEq/L with the range extending from 40 to 146 mEq/L. The average free acid for this group was 61.9 mEq/L, the range extending from 20 to 118 mEq/L. For the six females the average total acid was 71.1 mEq/L, the range extending from 40 to 120 mEq/L. The average free acid for this group was 52.0 mEq/L, ranging from 26 to 104 mEq/L.

Presence of retention: In 13 patients nausea and/or vomiting was mentioned in the history, but sufficient information necessary to determine whether this was due to retention or reflex was not present. Five patients had definite retention demonstrated either by x-ray or gastric residual volume. However, in 35 patients (66%) there was no history or objective evidence to suggest retention. Thus in the forty patients whose status as to the presence or absence of retention is known, 87.5 per cent had no evidence of such retention.

Complications: Twenty-eight patients (53%) experienced at least one hemorrhage, and nine of these experienced more than one. In each of two patients a single episode of duodenal perforation occurred. A third patient experienced three episodes of perforation, two from a duodenal, one from a prepyloric ulcer.

TABLE III
Distribution of Secretory Patterns in Response to 0.5 cc Histamine Phosphate

Concentration mEq/L	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	101-110	111-120	121-130	131-140	141-150
Total Acid . . .			3	1	3	1	4	3		2	2		1	1
Free Acid . . .	2	3	1	2	6	2		1		3		1		

Medical therapy: In 23 patients (43%) conventional medical methods of therapy were applied and were successful. It was our impression that in these cases there was no undue delay in response to therapy. Symptoms subsided within several days, and the gastric ulcer had disappeared on repeated gastrointestinal series.

Surgery: Thirty patients (57%) underwent gastrectomy, of which 29 were subtotal and one was total (the gastric ulcer having the radiological and gross appearance of a carcinoma). The indication for surgery in most of these cases was hemorrhage. The experience of our institution has been that the mortality of hemorrhage from gastric ulcer can be significantly reduced by early surgery, and because of this experience many patients underwent surgery. Three patients had closure of a perforation; two of these subsequently underwent subtotal gastrectomy. Among those patients who had definitive ulcer surgery, there was no instance of either marginal or recurrent gastric ulceration.

Mortality: There were four deaths in the series. One was due to peritonitis occurring in the postoperative period after subtotal gastrectomy. The other three were from causes unrelated to ulcer disease (uremia, pulmonary edema, and subsequent to urological surgery).

DISCUSSION

The incidence of combined ulceration differs depending on the source of the material. Feldman reviewing the literature prior to 1953, reported a composite incidence of 0.15% for x-ray studies and 0.32% for general autopsy studies (1). However, for autopsied peptic ulcer cases, the incidence was 6.5%, surgical ulcer cases 7%, and for all peptic ulcer cases the composite was 2.8%. The incidence of combined ulcer among benign gastric ulcer cases from all sources was 17.4%, and among duodenal ulcer cases was 5%.

In a more recent autopsy series, Watkinson found the incidence of combined ulcer to be 2.3% for males and 1.1% for females (2). In recent clinical series the incidence of combined ulcers among gastric ulcers has ranged from 12% to 38% (3, 4). Thus our incidence of 7.9% is less than most reported series. It is suggested that the incidence of duodenal ulcer associated with gastric ulcer in our series is very close to its incidence in the normal population, and the two may occur by coincidence, one not necessarily predisposing to the other.

The age at appearance of the combined ulcer and sex incidence of our series is similar to that of Mangold (3) and of Comfort (5), demonstrating a pattern with respect to these factors most resembling gastric ulcer.

Disagreement exists regarding the location of the gastric ulcer. Mangold's series considered only those cases in which the gastric ulcer was above the angulus (3). He assumed that an additional 25% occur in the pylorus. Billington's series suggested that in combined ulcers, at least in males, the gastric ulcer tended to be in the body more frequently than in simple gastric ulcers (6). However, Comfort reported that 57.8% of the gastric ulcers in the combined group were in the antrum (5). Our series supports the latter report in that among the combined ulcers almost half (42%) the single gastric ulcers occurred below the angulus. This is in contrast to simple gastric ulcers, which on the basis of roentgenologic data (7), are located, most often, at or proximal to the angulus, only about 26% occurring in the canal or prepyloric region.

That duodenal ulcer precedes the gastric ulcer in the great majority, more than two-thirds of cases, is consistent with other published series. The reason for this particular time sequence is not known. It has been implied that the etiology of the gastric ulcer is related to the preceding duodenal ulcer (8). However, it is also possible that this time sequence may merely reflect the fact that uncombined gastric ulcer occurs, on the average, a decade later than duodenal ulcer.

Since stasis has been advanced as an important factor in the etiology of gastric ulcer, it has been of interest to examine the role of pyloric obstruction in the pathogenesis of combined ulceration. The series of 135 combined ulcers reported by Johnson (8) in which there was evidence of stenosis in 64% is in marked contrast to Mangold's series (3) in which there was no evidence of any stenosis in 71.7%, and Angaard's series (4) in which 68 of 81 patients had no evidence of retention. Our finding that 66% had no indication of obstruction or retention supports the last two series, and suggests that, at least in most, pyloric obstruction is not the key factor in the etiology of the gastric ulcer.

The secretory values in our patients were in the normal range (9). Admittedly, acid concentration after submaximal doses of histamine is not the best test of secretory function. Johnson, on the basis of output of acid in overnight secretion, reported hypersecretion in patients with combined ulceration (10). Using the response to a "maximal" dose of histamine, Marks and Shay reported that the acid output was slightly greater than in normals, but lower than in simple duodenal ulcer patients (11). Studies by Sircus suggest that this may be true in males, but not in females (12). Ball, to the contrary, reported that there were only minor differences in secretory behavior between gastric ulcer patients who had an associated duodenal ulcer and those who did not (13). Whatever differences that were present appeared to be more pronounced in females.

Hemorrhage occurred in more than half (53%) of the patients in this series. Mangold's series has an incidence of 38% (3). Most series do not emphasize the frequency of this complication. The incidence of hemorrhage from a single ulcer derived from an average of three separate series, is reported as 28% in males and 32% in females for gastric ulcer, and 20% for males and 21% for females for duodenal ulcer (7). Thus the risk of hemorrhage in combined ulceration appears to be additive and is clearly greater than the risk from a single ulcer, either gastric or duodenal.

The high incidence of gastrectomy (57%) in this series attests to the severity of the course of combined ulcer disease. In addition to the frequency of hemorrhage, intractability of symptoms along with frequent exacerbations were indications for surgery in many of these patients. Several patients had surgery because of suspicion that the gastric ulcer was malignant, but this was an infrequent occurrence.

SUMMARY

In a review of records of 1435 peptic ulcer patients, 53 cases of combined gastric and duodenal ulceration were found, an incidence of 3.7%. Among gastric ulcers the incidence was 7.9%, and among duodenal ulcers the incidence was 3.2%.

The age and sex incidence was similar to that of gastric ulcer. Forty-two per cent of the gastric ulcers were in the antrum or prepyloric region, and 9% had multiple gastric ulcers.

The duodenal ulcer preceded the gastric ulcer in 64% of cases in which the time sequence was known.

The secretory tests of these patients appeared to be within the normal range.

In forty patients in whom the presence or absence of retention could be determined, 87.5% had no evidence of retention.

In 28 patients (53%) one or more hemorrhages had occurred, and three patients had suffered a perforation of an ulcer. Thirty patients came to surgery, the primary indication being hemorrhage. The anatomic features and clinical course and response to therapy, except for the frequency of hemorrhage, did not appear to differ from single ulcers.

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Clinico-Pathological Conference

EDEMA, ANURIA AND HYPERURICEMIA WITHOUT SEVERE AZOTEMIA

Edited by

FENTON SCHAFFNER, M.D.

New York, N. Y.

A 26 year old Negro male was admitted to The Mount Sinai Hospital because of anuria for one day.

He developed coryza and a sore throat 25 days earlier for which he was given penicillin and some tablets. About 10 days later his urine became dark and scanty. Soon after, dependent edema and dyspnea developed, progressed and became severe by the time of admission. Anorexia with occasional vomiting associated with coughing was described. Because of anuria he was admitted to City Hospital in Elmhurst where catheterization yielded no urine. His blood pressure was 106/74 and his pulse 110/min. He was severely orthopneic and had a puffy face and edema of the legs. His joints were deformed. Moist rales were heard in both lungs and the liver was enlarged. Electrocardiogram was said to show a right bundle branch block. His serum electrolytes were normal but CO_2 was 14 mEq/L and uric acid was 16.8 mg%. He was given 0.4 mg Cedilanid. He was transferred here for possible hemodialysis after less than one day at City Hospital.

For 9 years the patient had severe deforming arthritis involving his hands, wrists, elbows and knees. He had been studied in several hospitals and had been on prednisone for 2 to 3 years, stopping it abruptly two weeks prior to admission. The patient had been hard of hearing since the age of 16 and he shared a familial absence of proximal interphalangeal joints in the fingers and toes with his father and brother. His mother had rheumatoid arthritis. He had visited the outpatient clinic of City Hospital during the last 2 to 3 years. There his urinalyses were negative, his BUN was 11 mg%, and his hemoglobin was 11.5–13 Gm%. Serology and latex fixation were negative. Leukocytosis of 12,000 and 16,000 were recorded, and uric acid values of 4.5–7 mg% were obtained.

On examination he appeared acutely ill and orthopneic. Temperature was 100° , pulse 104/min and regular, blood pressure 95/65, and respirations 38/min. Positive findings were rales in both lung bases, heart enlarged to the left with P2 much louder than A2 and widely split, a protodiastolic gallop at the apex, a possible pericardial friction rub, slight hepatomegaly, edema up to the lower chest and of the hands and face, decubital ulcers on the sacrum and left greater

From the Department of Pathology, The Mount Sinai Hospital, New York.

trochanter, deformities of both hands, absence of proximal interphalangeal joints of finger and toes, and painful, swollen, warm wrists and elbows.

A very small amount of urine obtained by catheter contained many white blood cells and clumps and only a few red blood cells. Albumin was 3+ and the reaction acid. No bacilluria was noted. Hemoglobin was 12.5 Gm% and 9.8 Gm% the next morning. White blood count was 19,900/mm³ and 29,900/mm³ the next morning. Differential count showed only a leukocytosis with a left shift. Several BUN determinations were done and ranged from 37 to 50 mg%, the last just before death. Blood glucose was 117 mg%, CO₂ 20.2 mEq L, sodium 151 mEq L, and potassium 5.4-6.0 mEq L. Serum albumin was 2.0 Gm% and globulin 4.3 Gm%. Electrophoresis showed a low albumin, very low beta globulin and slightly elevated gamma globulin. Creatinine was 3.5 mg% and uric acid 17.4 mg%. Stools were guaiac negative and 2 LE preparations were negative. *B. pyocyaneus* was cultured from the urine although cultures from ureteral catheters and blood cultures were sterile. ASLO titer was 330 units.

X-rays revealed cardiac enlargement consistent with effusion, suggestion of right pleural effusion, somewhat larger than normal kidneys, and arthritic changes in the left hip joint. The patient was cystoscoped and catheters passed to each kidney with ease. A few drops of bloody fluid were obtained from the right side and about 5 ml of light colored urine from the left. The bladder was empty and the trigone was inflamed.

Electrocardiogram displayed a PR interval of 0.16 sec, QRS of 0.09 sec and QT of 0.4 sec at a rate of 100 min. Voltage was low throughout. A small R and deep S were present in lead I and a tall R and no S in VS was deep in a VL. ST and T were depressed and flat or inverted throughout.

After 18 hours in the hospital, blood pressure began to fall and coma supervened. Pericardiocentesis yielded 50 ml of serosanguinous fluid which was sterile. The patient expired after 22 hours in the hospital.

*Dr. Lester Tuchman**: We have what I think is an extraordinary case. This man, at the age of 26, reached the City Hospital at Elmhurst edematous, dyspneic and anuric, and the question was whether he was in primary heart failure or in primary renal failure in view of the total anuria.

I think the majority of the thinking was that this was essentially renal disease and that the obvious heart failure was secondary to the profound impairment of renal function. We were astonished when the laboratory reports came back to find that he did not have the marked azotemia that we were certain he would show. The CO₂ at City Hospital where he spent 18 hours before being sent here for possible dialysis, was 14 mEq L. To our great surprise, the uric acid was 17 mg%. The other findings were not remarkable.

He was not hypertensive. In fact, he was on the borderline of shock. His blood pressure levels varied between 90 and 100 mmHg. He elaborated no urine at all during the time he was at the City Hospital. He was febrile. He had an infection of decubitous origin. We assumed, I think, that what he had was an unusual manifestation of glomerulonephritis. In an attempt to put all these

* Attending Physician for Special Service, The Mount Sinai Hospital, New York.

things together under one heading, among the things considered were lupus erythematosus or periarteritis which would account for the long-standing rheumatoid arthritis documented for at least seven years, the evidence of which was seen on the x-ray films.

Thinking as we always do of the possibility of iatrogenic disease, a careful analysis of the drugs he had been taking revealed nothing more than prednisone, which he had had in fair doses in order to maintain relative comfort as far as his arthritis was concerned but which had been stopped about two weeks before he came to the hospital.

The immediate antecedent history was one of respiratory disease, shortness of breath, followed by some edema which was largely dependent, although he had one or two days of puffiness of the face at the very onset.

The thing that distressed him most was the tremendous dyspnea and orthopnea and rapid evolution of massive peripheral edema. The scanty urine he just noticed in passing, but the total anuria in his hospital stay was what impressed us most.

Thinking that possibly he might benefit from dialysis, since this might have been a disturbance of tubular function subsequent to a period of shock, we sent him to The Mount Sinai Hospital where on admission the findings at the City Hospital were corroborated.

The blood uric acid level of 17 mg% made some people feel that possibly he had uric acid calculi leading to mechanical obstruction. The ureters were therefore catheterized but neither evidence of obstruction nor of urine production was obtained.

During the entire time he was here, 5 ml of what may have been urine was found and it contained a heavy protein admixture, but no formed elements.

The man died in terminal pyrexia. He was obviously additionally suffering from infection due to decubitous ulcers though blood culture was negative. When he died, I think the majority opinion was that he had primary renal disease and the minority opinion was that he had primary heart disease.

There were some important negative findings. This man had a normal blood uric acid several months before he was hospitalized. He was studied in an outpatient department for years for the treatment of rheumatoid arthritis so that we have no evidence of antecedent renal disease and no evidence of antecedent myocardial disease.

A chest x-ray taken two years before admission showed very slight enlargement of the heart, if any. A film taken on the day before he died and a film taken here the day he died showed transverse enlargement of the cardiac silhouette. This is either dilatation alone or dilatation and pericardial fluid. My feeling is that a great deal of it was probably dilatation and maybe some hypertrophy.

I am not able to explain the high blood uric acid level. This is why we asked Dr. Gutman, who is an authority on uric acid, to tell you what he thinks it may be due to. The literature mentions that lymphoma, even one that otherwise is not suspected, can give elevated blood uric acid levels as an outstanding finding.

What we have to ask Dr. Zak to explain are: Did his kidneys fail because his heart failed, or did he go into heart failure because of acute glomerulonephritis? What we must ask Dr. Gutman to tell us is why he had a high blood uric acid level. He could not have had chronic glomerulonephritis because we know he had good kidney function prior to the terminal episode, and x-rays show they are normal in size. Total anuria occurs in only a small percentage of patients with acute glomerulonephritis, and he had no hypertension and no severe azotemia. If he had primary myocardial disease which is common in young Negroes, then why this complete and utter collapse of renal function?

*Dr. Alexander B. Gutman**: The question referred to me was: Why should the serum uric acid level be 17 mg% with no obvious cause? This was not quite the situation here, but let us consider that proposition first. A uric acid level that high is unusual and is not seen in gout, for example. Levels reaching 12 mg% in gout are extremely high indeed in the absence of renal disease. Part of the nitrogen retained in renal disease is uric acid nitrogen. When no renal disease is recognizable and uric acid levels are this high, one has to think of overproduction which ordinarily means polycythemia, myeloid metaplasia or lymphoma, in which there is an increase in nucleic acid production and turnover. We have seen young people with Hodgkin's disease treated with nitrogen mustard who have had serum uric acid levels as high as 40 mg%.

In the present case we have to consider seriously the possibility that the rise in uric acid was related, at least in part, to renal disease, although throughout the rise in uric acid is disproportionate to the rise in blood urea nitrogen. There are two possible explanations. First, serum uric acid may have been high to start. Any superimposed renal impairment might result in excessively high uric acid levels in the blood. We are told that the uric acid levels in the clinic in which he was followed varied between 4.5 and 7.0 mg%. That is quite a variation. Values between 6.0 and 7.0 mg% would constitute hyperuricemia, depending also on the method employed.

Renal damage can exist in which the BUN is not very high and the uric acid is disproportionately elevated. This situation is seen, for example, in toxemias of pregnancy and has caused a great deal of speculation as to the mechanism. Studies of nitrogen 15 incorporation into uric acid in such patients indicate that formation of uric acid is not increased and probably the hyperuricemia of that disorder is related to renal disease. We would have to postulate that the lesion is largely tubular and to a lesser extent glomerular.

We think now that active tubular secretion of uric acid occurs, so it is quite conceivable that a tubular lesion, if it were localized in the right place, presumably the proximal tubule, might produce hyperuricemia without much increase in BUN. I would have to assume that there was rather extensive tubular damage in this case.

Other possibilities are intriguing and should be mentioned in passing. Some underlying congenital disease of the kidneys may have been present because of the association with deafness which appeared at the age of 16, although I

* Director, Department of Medicine, The Mount Sinai Hospital, New York.

was told it followed otitis media. If it were familial and appeared earlier, one might think of the association of deafness with certain peculiar renal lesions with foam cells which may produce serious renal insufficiency. Another congenital abnormality is developmental anomalies of the joints with superimposed rheumatoid arthritis, which might affect some of the viscera. Therefore, in answer to your question, Dr. Tuchman, I think since we are dealing with some form of renal disease, it would be prudent to associate the rise in serum uric acid with the renal disease, in which case I would expect a good deal of tubular damage. We are not sure but what this was superimposed on an initial hyperuricemia of moderate degree.

Dr. Tuchman: The thing I have difficulty with is the fact that there is no evidence whatever of any antecedent renal damage. Therefore, if it is renal disease, is it an acute process? There was so much that is totally atypical to the usual course of acute glomerulonephritis. I think that Dr. Zak will show us a good deal of myocardial disease, possibly a lymphomatous disease which would, taken together, explain this otherwise odd group of symptoms all superimposed upon rheumatoid arthritis, *sui generis*, or upon arthritis as part of a diffuse collagen disease.

Physician: Was he given any diuretics?

Dr. Tuchman: This is something that we thought of and the answer is unequivocally no.

Dr. Frederick G. Zak:* Dr. Gutman, do the fluctuations of uric acid levels secondary to salicylate dosage (1) depend on the dosage?

Dr. Gutman: There is a possibility that he received salicylate treatment for rheumatoid arthritis. We know that the usual analgesic doses of salicylate that are given for arthritis are very likely to cause some increase in the serum uric acid level, and this may have been responsible for this initial hyperuricemia.

Dr. Zak: Let me first make a few points about some of the gross findings. The proximal interphalangeal joints were not present and therefore his fingers were straight (Fig. 1).

I was not able to find in the literature any connection of this malformation with any systemic or particularly renal disorder. Therefore, we have to accept this as an interesting but not integral facet of the case.

We removed synovial tissue from the shoulder joint and, to our surprise, the histological picture showed a good deal of acute inflammation with polymorphonuclear leukocytes usually found in flare-ups of rheumatoid arthritis (Fig. 2). This fits quite well with the fact that the patient was taken off his steroid maintenance about two weeks prior to his admission. In this hospital it was also noted that the joints were red and swollen.

At autopsy we saw exceedingly large superficial and deep lymph nodes. Some axillary nodes were up to 3 cm in diameter (Fig. 3). The junior members of the department, perhaps fortified by the clinical suggestion of lymphoma and the high serum uric acid level, felt that this was a lymphomatous disease. This was strengthened by the gross appearance of the enlarged spleen (Fig. 4).

* Associate Attending Pathologist, The Mount Sinai Hospital, New York.



FIG. 1. Congenital deformity of fingers.

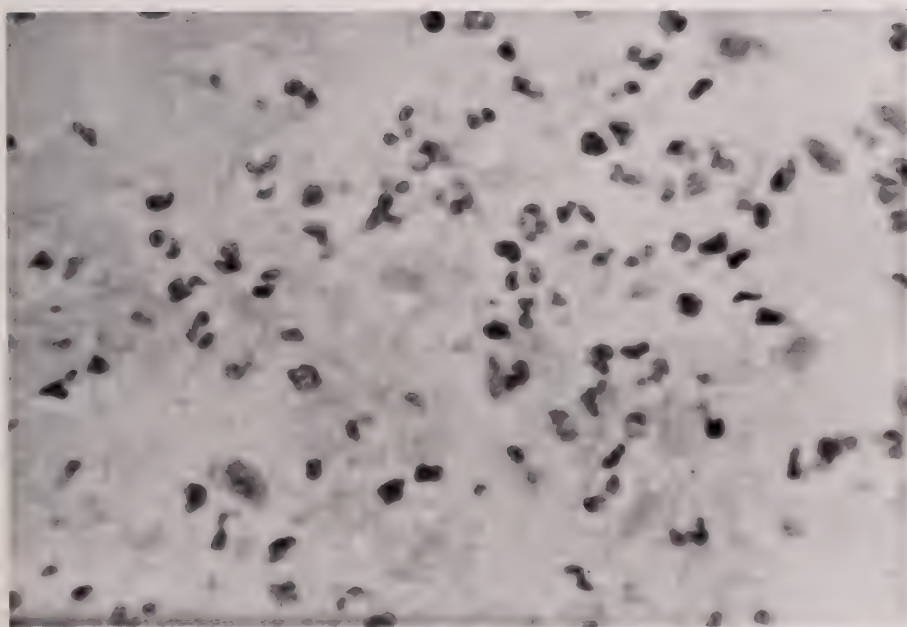


FIG. 2. Microscopic section of synovia showing acute arthritis. (H & E $\times 240$)

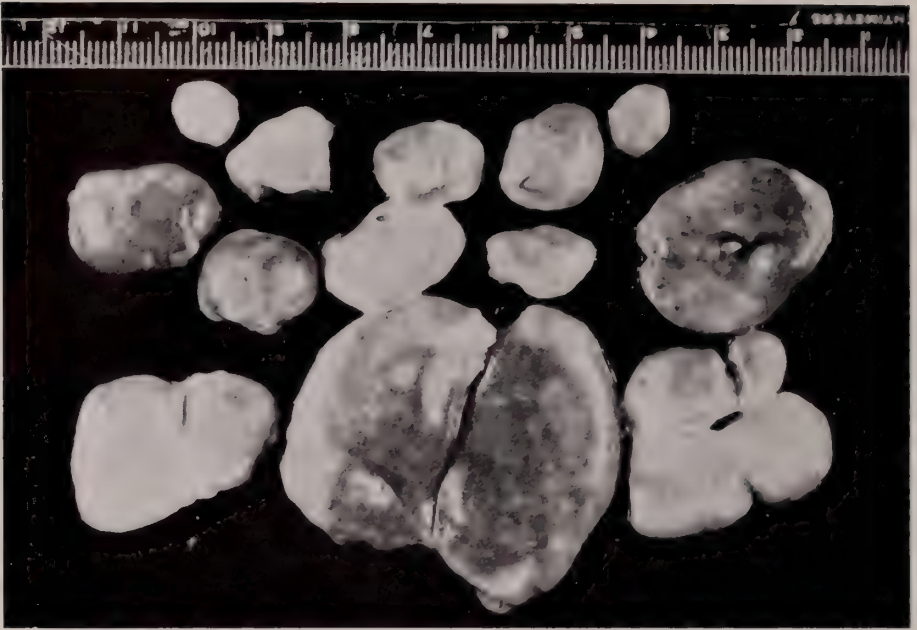


FIG. 3. Enlarged and hyperemic axillary nodes.

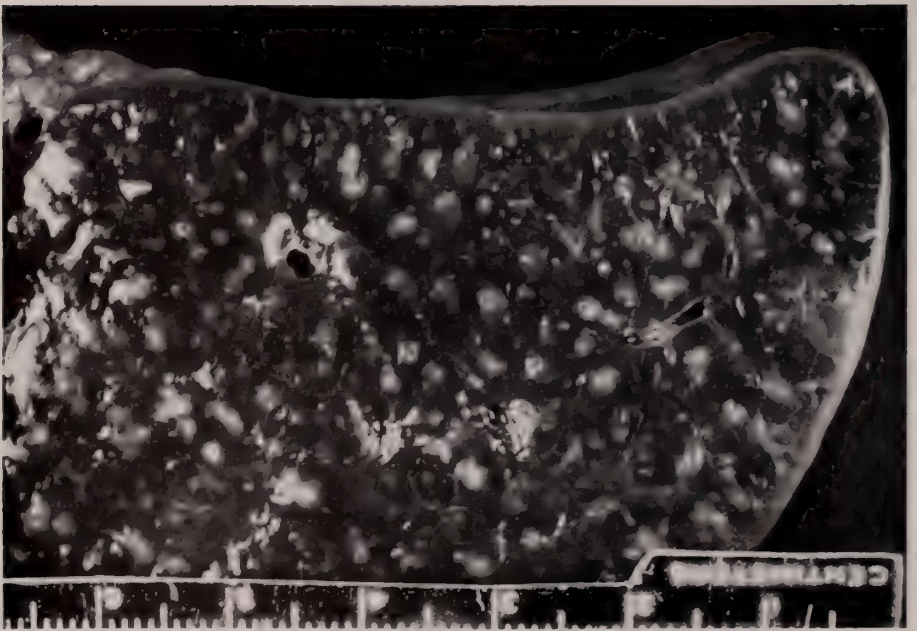


FIG. 4. Cut surface of enlarged spleen showing increased size of lymph follicles.

The lymph nodes were quite enlarged with an accentuated architecture and an increased number of very prominent follicles. Although polymorphonuclear leukocytes were in the medullary cords, plasma cells predominated. Large lymph nodes, with plasma cells, have been described in rheumatoid arthritis, and the fact that this was not only in the bronchial nodes, where plasma cells occur frequently, but also in the peripheral and abdominal lymph nodes lent support to the interpretation that this was reactive plasmacytosis as seen in chronic rheumatoid arthritis.

The heart was covered by a shaggy exudate which was partly hemorrhagic. I would go along with the interpretation of a uremic pericarditis. However, I have a number of reservations. One is that he really was not uremic. Secondly, he was a patient with rheumatoid arthritis. Rheumatoid pericarditis may be precipitated by steroid withdrawal (2). Finally, the histologic picture, although not specific in this particular instance, could be interpreted as pericarditis of longer than a few days' duration (Fig. 5).

The fluid in the pericardium was estimated to be about 100 ml. Therefore, I do not feel that the pericardial effusion contributed much to his cardiac failure. The left ventricle was considerably enlarged and thickened. The aortic and mitral valves were normal. This man never had hypertension and yet he had a large heart weighing 470 Gm. despite the fact that he was bedridden for many years. The right heart likewise contributed to the cardiac hypertrophy with a thickened right ventricle. The valves were delicate and normal and the outflow tract of the right ventricle was not a site of stenosis. In rheumatoid arthritis, rheumatic valvular changes are frequently found. They were absent here. We feel, therefore, that this large heart in a young Negro male may fall into a group of cases described from this hospital in 1955, Dr. Tuchman being one of the co-authors, under the name of cardiac hypertrophy and insufficiency of unknown etiology.

By exclusion of valvular disease, hypertension, coarctation, extensive myocarditis or arteriosclerosis with or without infarction, there remains a group of patients with otherwise unexplained cardiomegaly. This is more commonly found in Negroes.

One of the important facets of this malady is that these people tend to go into cardiac failure.

Microscopically, this patient had some focal inflammatory infiltrates in myocardium and endocardium, not enough to call it a diffuse myocarditis, and part and parcel of his rheumatoid disease (3) (Fig. 6).

Involvement of large serous cavities other than the pericardium occurs commonly in rheumatoid arthritis. Fibrous adhesions were present in pleural sacs. On the surface of the liver, extensive fibrous and fibrinous adhesions were found (Fig. 7).

The liver, pancreas and spleen showed advanced long standing passive congestion. This man's spleen had some congenital fissures and weighed 475 Gm. Whitish nodules which the prosector interpreted as lymphoma, probably Hodgkin's disease, were seen on the cut surface. These were actually very enlarged

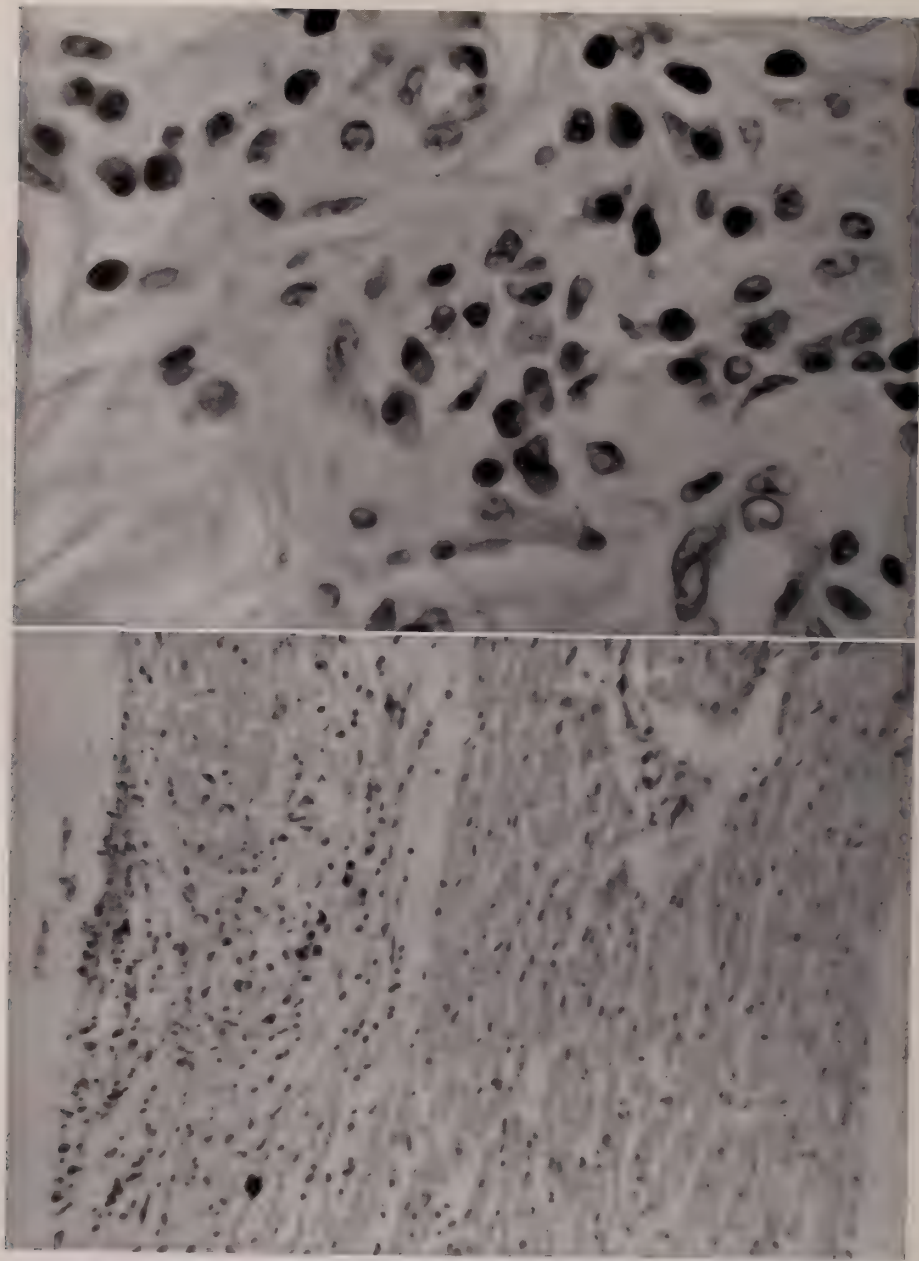


FIG. 5. Plasma cellular infiltrate in pericardium. (H & E \times 400)

FIG. 6. Focal subacute carditis. (H & E \times 63)

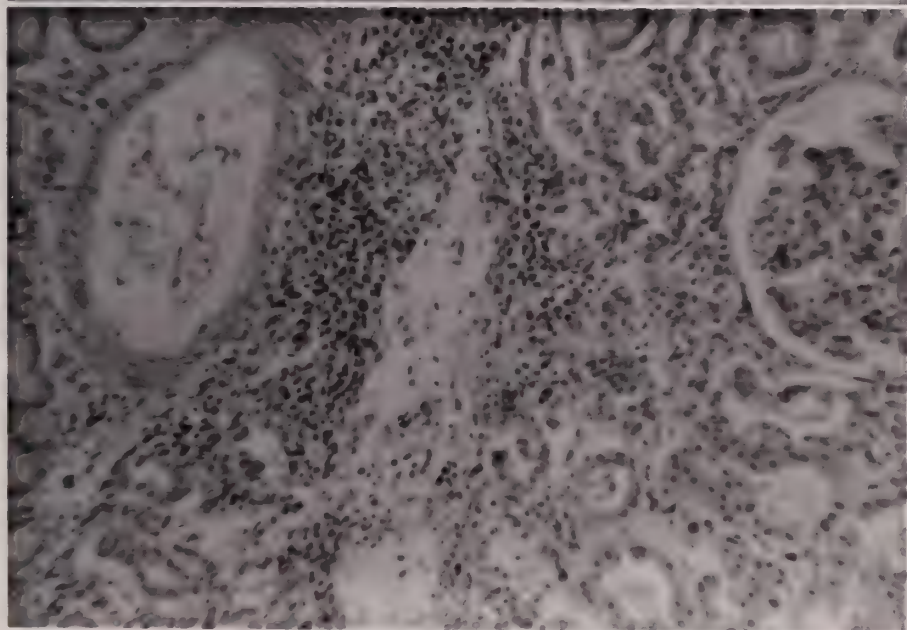


FIG. 7. Organizing perihepatitis. (H & E $\times 63$)

FIG. 8. Interstitial nephritis. (H & E $\times 120$)

follicles, the result of his chronic rheumatoid arthritis in addition to his youth. Splenomegaly is clinically present in some cases of rheumatoid arthritis, e.g. Still's disease and Felty's syndrome, and at autopsy large spleens with prominent follicles are found. Histologically, the spleen contained increased polymorphonuclear leukocytes, eosinophiles, and particularly numerous plasma cells, again evidence of his rheumatoid arthritis. However, the spleen also showed chronic passive congestion as one of the factors accounting for its increase in size and its reddish appearance. The adrenals were thin and depleted of lipid in many areas partly as a result of steroid therapy. Some years ago a report from the British West Indies stated that the native population there had adrenal weights of far less than those of Europeans or Americans, and that they withstood stress much less well than the white population in the same area.

Perhaps lack of response to stress may have contributed to his acute demise.

The radiologist reported enlarged kidneys. They weighed 275 Gm. each, the normal weight being about 150 Gm. Therefore, they were almost double their size and they were quite swollen.

On the cut surface, fine yellow dots and streaks were seen. Some of the dots appeared cystic and microscopically they were indeed cystic areas which contained old pus with broken down polymorphonuclear leukocytes and cholesterol crystals attesting to their age. This had nothing to do with the present disease but was a microscopic malformation which he had only in the outermost surface of the kidney in very local areas and therefore had no bearing on his renal failure.

The spaces between the tubules were widened as a result of a considerable amount of interstitial edema which was the main cause for the swelling of the kidney. There was no glomerular disease of any consequence present. We were therefore not dealing with an acute glomerulonephritis. We did find scattered throughout the kidney in rather impressive accumulations, particularly along vessels and mainly along the veins, an infiltrate consisting of a variety of cells, among them plasma cells (Fig. 8). This infiltrate was similar to that which he had in his heart, spleen and lymph nodes. While this may be part of his rheumatoid disease, I feel that it may be interpreted in another way, namely, as an instance of so-called acute interstitial nephritis of scarlet fever (4). In the past this used to be a very common cause of death in scarlet fever cases early in their course.

I hasten to add that this lesion is not specific for scarlet fever. However, it is most classically seen and usually appears within the first week following scarlet fever whereas the glomerulonephritis comes about three weeks after the onset of the scarlet fever.

The term acute interstitial nephritis refers to both the cellular and the serous exudate. Poisons and drug reactions accompanied by decreased renal blood flow such as the sulfonamides (5), produce changes which histologically are indistinguishable from scarlet fever nephritis. Various bacterial, rickettsial and viral diseases, particularly streptococcal, e.g. erysipelas, have been described to cause this type of nephritis. This man had a sore throat and ten days later

he became anuric. He also had infected wounds in the form of decubitus ulcers. Unfortunately, no bacteriologic examination was available either from his throat or from his wounds. However, his ASLO titer was elevated.

This man who had familial skeletal anomalies also had rheumatoid arthritis from which his mother suffered. Apparently he also had cardiomegaly as described by Elster, Horn and Tuchman, and he was in long standing cardiac failure, as evidenced by the morphological changes of liver and pancreas. This produced decreased renal blood flow.

However, he managed to hold his own until he developed a sore throat presumably due to streptococci. Ten days later he became oliguric. Pathologists tend to explain things in a rather simple mechanical way, and one of their explanations for acute renal shutdown is swelling of the kidney. The kidney is encased in a thick fibrous capsule and when it swells it will interfere with its own drainage like a glaucomatous globe. It appeals to me because it is such a simple explanation, particularly when tubular necrosis was not demonstrable histologically. Swelling of the kidneys caused further impairment of renal blood flow and was followed by oliguria and azotemia.

Dr. Tuchman: This brilliant presentation leaves me a little dissatisfied in this respect: We have been so spoiled by the pathologists in expecting to have the answers to all questions that in the rare instances where I think the problem remains, we feel that we have somehow been let down.

Apropos of primary heart disease, the contribution that Dr. Horn, Dr. Elster and I made was a small one (6). We were not the first to describe it but we think we did make one small contribution though, which was to keep away from the old name of idiopathic cardiac hypertrophy which presupposes that it is an entity and tends to prevent thinking about etiology.

It is a common disease in parts of the world; for instance, it is one of the commonest causes of heart failure in Africa. It is a progressive disease in which the primary change is in the heart muscle fiber causing the heart to dilate and hypertrophy, following which the endocardium thickens. Mural thrombi develop on the endocardium and when they embolize, fever is produced. If it is seen during this phase, somebody will call it myocarditis. We counted about thirty different terms under which it has been described, but the salient feature is that it occurs in young people frequently, mainly young Negro males. Rapid and frequently irreversible heart failure supervenes and I think this is what happened here.

We know he had a normal sized heart only shortly before he was sick. Upon this condition of cardiac hypertrophy, dilatation and muscle failure were superimposed heart failure and shock, and all these things together combined to give this picture which I have not seen before.

There seems to be no question of that in my mind, from Dr. Zak's presentation, that the heart failure was primary and that renal failure was superimposed.

I would like to know why, with complete anuria, he developed neither hypertension nor elevation of his blood urea nitrogen.

Dr. Zak: The main point that I want to make is, the next time you see a pa-

tient with a sore throat who goes into a renal shutdown ten days later, think of acute interstitial nephritis.

Physician: Dr. Zak, since the inflammatory process here was made up of a peculiar combination of cells, plasma cells, eosinophiles and lymphocytes, and since this was found everywhere that you looked, instead of calling this process inflammation, would this fit into some kind of neoplastic process?

Dr. Zak: That is the argument that I also brought forward and put back again. The inflammatory infiltrate is just due to his rheumatoid arthritis. However, in cases of scarlet fever nephritis and others, in the absence of rheumatoid arthritis, the infiltrate in the kidney is typically described as one of plasma cells, lymphocytes and eosinophiles. Under the low magnification, the kidney infiltrate may look like a lymphatic leukemia or lymphosarcoma.

Dr. Gutman: In reconstructing this case, I would follow your plan quite closely. Certain genetic liabilities were present which were expressed morphologically in the failure of certain joints to develop. Included in this would be a susceptibility to rheumatoid arthritis, as you indicated, because some forms of it are transmitted genetically. He had severe rheumatoid arthritis early in life and produced cellular infiltration that you showed. One of the forms of heart disease that occurs as a variant of that described by Dr. Tuchman is a familial cardiomyopathy. Have you ruled this out altogether?

Dr. Zak: There was no evidence by history of large hearts in any of the other members of the family or of premature cardiac deaths. We must consider this a possibility, however, since this man was stigmatized from the maternal side with rheumatoid arthritis and from the paternal side with his peculiar joint deformity. He may very well be a member of a family who had some type of heart disease but we have no definite information.

Final diagnoses:

1. ACUTE INTERSTITIAL NEPHRITIS AS SEEN IN SCARLET FEVER, WITH RENAL SHUTDOWN AND SWELLING.
2. FAMILIAL RHEUMATOID DISEASE WITH ENLARGEMENT OF SUPERFICIAL AND DEEP LYMPH NODES, SPLENOMEGALY (FELTY'S SYNDROME), AND WIDESPREAD PLASMACYTOSIS; RHEUMATOID POLY-SEROSITIS, OLD OR RECENT (PLEURAE, PERICARDIUM, LIVER); FOCAL DISSEMINATED RHEUMATOID MYOCARDITIS, SUBACUTE.
3. "CARDIAC HYPERTROPHY AND INSUFFICIENCY OF UNKNOWN ETIOLOGY" WITH CHRONIC PASSIVE CONGESTION OF LIVER, SPLEEN, PANCREAS.
4. FAMILIAL SKELETAL ANOMALY OF DIGITS (ABSENCE OF PROXIMAL INTERPHALANGEAL JOINTS).
5. MULTIPLE RENAL CYSTS, MINUTE.
6. OLD PULMONARY EMBOLUS, LEFT UPPER LOBE.

ADDENDUM (Dr. Zak)

On the background of familial long lasting and crippling rheumatoid disease, there is engrafted an acute upper respiratory infection, presumably strepto-

coecal because of the ASLO titer rise. Ten days later, oliguria developed. This short time interval is typically seen in the acute interstitial nephritis of scarlet fever and militates against the diagnosis of acute glomerulonephritis. While no positive information is available from two family physicians as to sulfonamide treatment at this time, this cannot be ruled out. The microscopic picture of sulfonamide nephritis may be indistinguishable from the postscarlatinal acute interstitial nephritis. Steroid therapy was stopped shortly after, allowing for a flare-up of joint symptoms verified histologically and the appearance of rheumatoid serositis (pericarditis, perihepatitis) and carditis. The interplay of chronic heart failure, based on idiopathic cardiomegaly (possibly familial) with added more acute failure caused by rheumatoid carditis secondary to steroid withdrawal on one hand and acute interstitial nephritis led to decreased renal perfusion, oliguria, anasarca and death. The hyperuricemia cannot be explained on the basis of salicylate therapy, as there was none, but is possibly an accompaniment of the steroid withdrawal in a patient with striking lymphocytic and plasmacytic hyperplasia.

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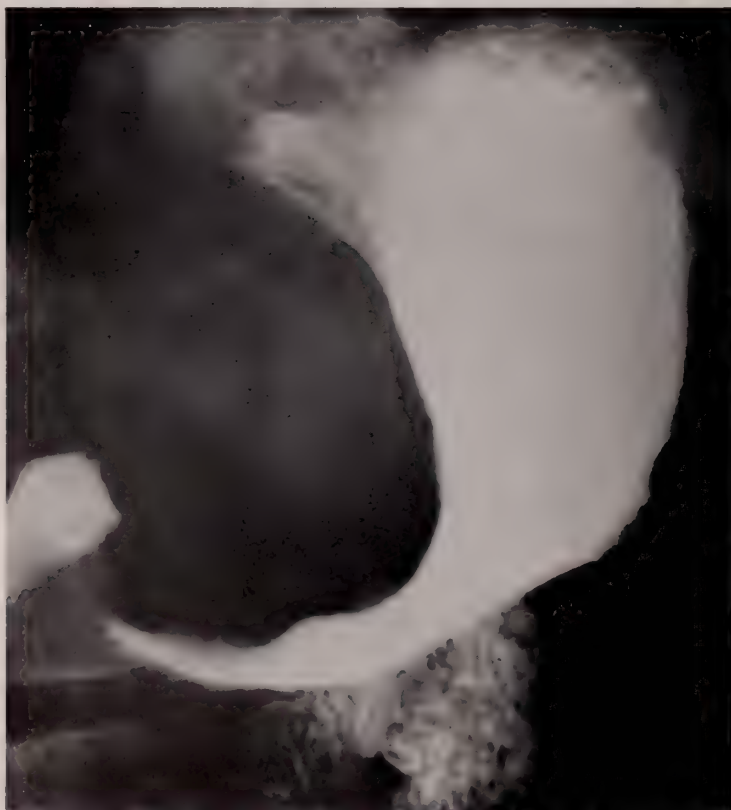
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Radiological Notes

CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D., *Co-Editors*
New York, N. Y.

CASE NO. 179

A 48 year old female underwent radical mastectomy four months before admission for an infiltrating carcinoma of the right breast with lymph node involvement and invasion of the axillary vein. Postoperatively, the patient was



Case 179, Fig. 1. The entire distal two-thirds of the stomach is conically narrowed. There is rigidity along both curvatures and the mucosal folds are effaced. The stomach empties well.

given radiotherapy to the right axilla and supraclavicular fossa. During the course of radiotherapy, the patient had an inordinate amount of nausea and

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

vomiting associated with epigastric pain. Because of these symptoms, an upper gastrointestinal tract examination was performed. The esophagus was normal. The stomach was noted to be diffusely infiltrated and markedly narrowed, especially in its lower two-thirds (Fig. 1). Both curvatures were rigid and the mucosal folds were effaced, but no discrete ulcerations were identified. The stomach emptied quickly. No extrinsic masses were noted around the stomach. The duodenal bulb, duodenal sweep and remainder of the small intestine appeared normal.

Because of the inability to rule out a primary gastric neoplasm roentgenologically, laparotomy was performed. At operation, diffuse carcinomatosis was noted throughout the peritoneal cavity. The stomach, liver, ovaries and tubes were biopsied and revealed scirrhus carcinoma. No further procedures were performed. A follow-up gastrointestinal x-ray performed six months later revealed no change in the appearance of the stomach. Diffuse metastatic bone involvement of both lytic and sclerotic nature was identified.

Case Report: METASTATIC INVOLVEMENT OF THE STOMACH FROM PRIMARY CARCINOMA OF THE BREAST.

See discussion after Case No. 181.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Samuel H. Madell.

CASE NO. 180

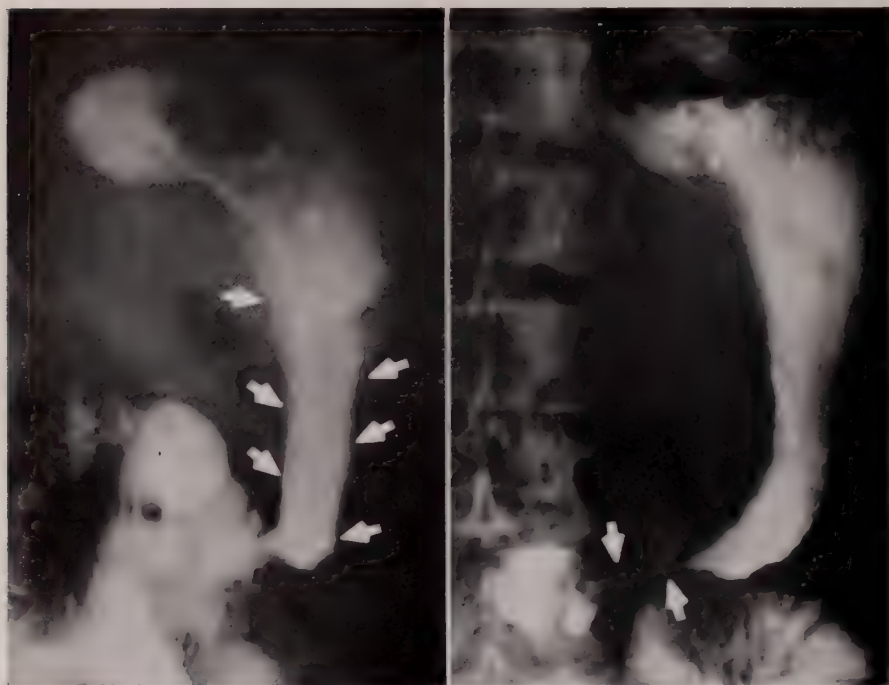
A 46 year old woman underwent left simple mastectomy and axillary node dissection for an infiltrating adenocarcinoma of the breast. One year later she developed a right pleural effusion which was treated with thoracenteses and instillation of nitrogen mustard. At the same time hysterectomy and bilateral salpingo-oophorectomy were performed. At laparotomy, extensive peritoneal metastases were noted with numerous nodules measuring from pinhead to pea size. The patient was then placed on testosterone and received radiotherapy directed to the pelvis. The patient had multiple bone metastases involving the dorsal and lumbosacral spine, with collapse of the 5th dorsal vertebral body. After surgical castration and maintenance hormone therapy, the patient's general condition improved markedly. One year later, because of the development of post-prandial fullness, nausea and loss of appetite, an upper gastrointestinal tract examination was performed.

The esophagus was normal. There was no delay to the passage of barium from the esophagus into the stomach. The contours of the distal two-thirds of the stomach, including the entire antrum, body and the lesser curvature of the fundus, were noted to be rigid (Fig. 1). The caliber of the stomach was reduced to approximately one-third of its normal size. In spite of the administration of a considerable amount of barium, it was impossible to distend the involved portions of the stomach. There was effacement of the rugal folds throughout the stomach, but no discrete ulcerations or intrinsic masses were noted. There was no evidence of extrinsic pressure upon the stomach. The gastric antrum was eccentrically narrowed and only a small amount of barium was able to pass

through it at any time; there was no evidence of gastric retention (Fig. 2). The duodenal bulb and sweep were normal as was the remainder of the small intestine.

Case Report: METASTATIC INVOLVEMENT OF THE STOMACH FROM PRIMARY CARCINOMA OF THE BREAST.

See discussion after Case No. 181.



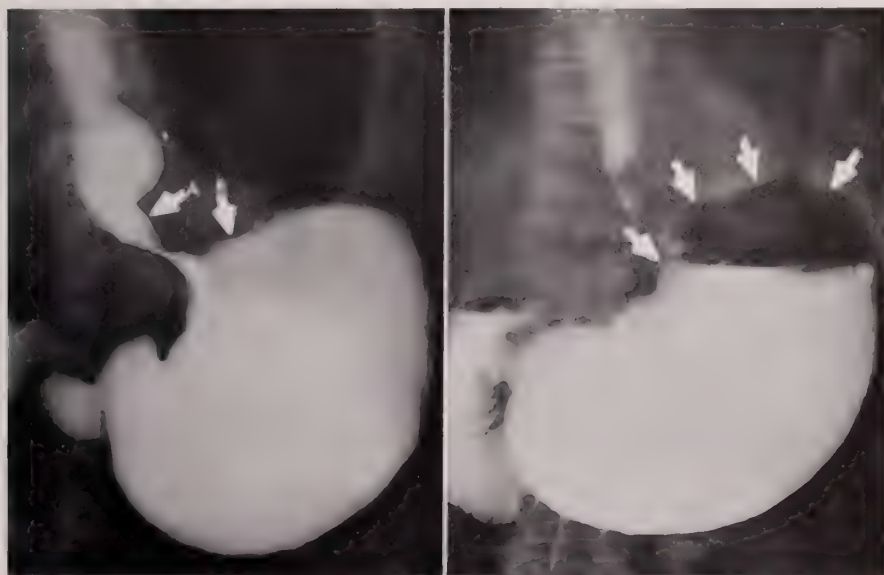
Case 180, Fig. 1. The contours of the distal two-thirds of the stomach are markedly narrowed and rigid (between arrows). The mucosa is effaced, but no discrete ulcerations are seen.

Case 180, Fig. 2. In the upright position, the stomach is again noted to be rigid. The antrum is maximally narrowed (between arrows). Also noted are extensive lytic and blastic metastases in the visualized lumbar vertebral bodies.

CASE NO. 181

A 66 year old female underwent right radical mastectomy for an infiltrating carcinoma of the breast, with one involved axillary lymph node. The patient received postoperative radiotherapy to the axilla and supraclavicular region, as well as to the internal mammary chain on the right side. She was well until four months before her last admission, when she noted difficulty in swallowing, postprandial abdominal discomfort, nausea and regurgitation. During this same period of time, the patient lost twenty pounds. She noted dysphagia for solids and limited her diet to puréed foods and liquids. Physical examination revealed

an acutely and chronically ill woman in moderate distress with signs of extensive recent weight loss and mild dehydration. There were no palpable axillary, supraclavicular or cervical nodes. The area of the right mastectomy revealed no local recurrence. There were signs of a left-sided pleural effusion extending to the upper third of the chest. No masses were felt in the epigastrium and there was no abdominal organ enlargement.



Case 181, Fig. 1. There is a discrete indentation upon the lateral aspect of the distal esophagus (arrow A) which narrows its lumen and causes a temporary delay to the passage of barium. There is no proximal dilatation of the esophagus. The gastric fundus is likewise involved by this intrinsic process (arrow B). A large left pleural effusion is noted.

Case 181, Fig. 2. When the proximal portion of the stomach is maximally distended with barium and gas, the entire fundus is noted to be involved by an extrinsic mass closely associated with its wall and causing considerable decrease in distensibility (arrows).

In order to elucidate the nature of the patient's dysphagia and abdominal discomfort, an upper gastrointestinal tract examination was performed. There was slight delay to the passage of barium through the lower end of the esophagus. There was evidence of extrinsic pressure localized upon the lateral aspect of the lower 3 cm of the esophagus, which extended along the cardia to involve the medial portion of the fundus of the stomach (Fig. 1). There was limited distensibility of the lower esophagus and fundus of the stomach, but no discrete ulceration or nodularity could be demonstrated. A barium tablet measuring 12 mm in diameter was held up just above the cardia for a period of 15 minutes and entered the stomach only after disintegration. There was evidence of extrin-

sic pressure upon the lesser curvature aspect of the stomach in its upper one-third, and attempts to maximally distend the proximal portion of the stomach with a combination of barium and gas (Fig. 2) revealed considerable reduction in the size and distensibility of the entire fundus. No other abnormalities were noted within the stomach, duodenum or small bowel. There was evidence of a large left pleural effusion.

Case Report: METASTATIC INVOLVEMENT OF THE STOMACH FROM PRIMARY CARCINOMA OF THE BREAST.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Frederick King.

DISCUSSION

CASES 179, 180, 181

Metastatic lesions to the stomach from any primary malignancy are very rare. Willis found that the stomach was involved by metastatic carcinoma in only two cases in 5,000 studied at autopsy (1). Stout described two instances of chorioepithelioma which showed metastatic involvement of the stomach (1). We have recently seen two cases of malignant melanoma which metastasized submucosally to the stomach and the small intestine. On occasion, widely disseminated carcinoma of the lung has been known to metastasize to the stomach, and more commonly to the small intestine.

Review of the literature reveals a very low incidence of metastases to the stomach from primary carcinoma of the breast. This rarity may be more apparent than real, in that when careful autopsies are performed in patients dying of metastatic carcinoma of the breast, the finding of gastrointestinal, and particularly gastric metastases appears to be more frequent than expected. Saphir reported three cases of metastatic involvement of the stomach in 43 consecutive autopsies of patients dying of carcinoma of the breast (2). Warren and Witham, however, found no cases of gastric involvement from metastatic carcinoma of the breast in 162 autopsies (3). Hartmann recently studied the autopsy material at the Memorial Hospital and divided the cases into two groups: those dying before 1949 and those from 1956 to 1959 (3). Before 1949, he found only seven cases of metastatic involvement of the stomach in 137 autopsies of patients who died of metastatic carcinoma of the breast. In 1956 to 1959, he reviewed 204 autopsied patients. He found 38 patients (18%) who showed metastatic involvement of the stomach. He raised the possibility that there has been an increased frequency of metastatic involvement of the gastrointestinal tract from carcinoma of the breast since the advent of corticosteroids. Dividing his 204 cases into 136 who had received steroids and 58 nonsteroid-treated patients, he found a significant difference in the number of patients who had intrinsic metastatic involvement of the stomach with mucosal ulceration and submucosal involvement. When the stomach was involved in the nonsteroid-treated patients, the lesions were limited to the serosa of the stomach and did not involve the

mucosa and submucosa. Since the steroid-treated patients did not live significantly longer than the nonsteroid-treated patients, he did not believe that this increase in incidence of mucosal and submucosal involvement was due to the longer duration of the disease. Instead, he and others have postulated that the administration of steroids predisposes to the dissemination of the carcinoma by decreasing local tissue resistance of the gastrointestinal mucosa and submucosa. This may be due to the drug's depressing effect on granulation tissue and gastric mucous production, and by its inhibition of the normally rapid regeneration of the gastric epithelium. Another causative factor may be a secondary decrease in the activity of the reticulo-endothelial system and a decrease in circulating antibodies.

In Cases 179 and 180, the stomach appears to be intrinsically involved, indistinguishable from the usual primary infiltrating scirrhus carcinoma of the stomach. Although in the first case laparotomy was performed and multiple biopsies were taken which showed scirrhus carcinoma, there is still a possibility that the scirrhus carcinoma represented a second primary neoplasm in the stomach with widespread metastases. This is unlikely in view of the type of bone metastases which developed later and which resembled the usual type of breast metastases. In Case 181, the involvement of the proximal third of the stomach is mostly extrinsic in type with only secondary involvement of the serosa by the exogastric metastasis. It is interesting to note that, in spite of Hartmann's observation, none of the three patients described in this report had received steroid therapy during the course of their illness.

From the three cases described, it is suggested that when a patient suffering from metastatic carcinoma of the breast develops severe upper gastrointestinal symptoms, the possibility of esophageal or gastric metastases should be entertained. It is possible that this complication is more frequent than was previously believed, especially since the advent of steroid therapy in metastatic carcinoma of the breast. When the stomach is intrinsically involved, it is indistinguishable radiologically from primary scirrhus carcinoma of the stomach.

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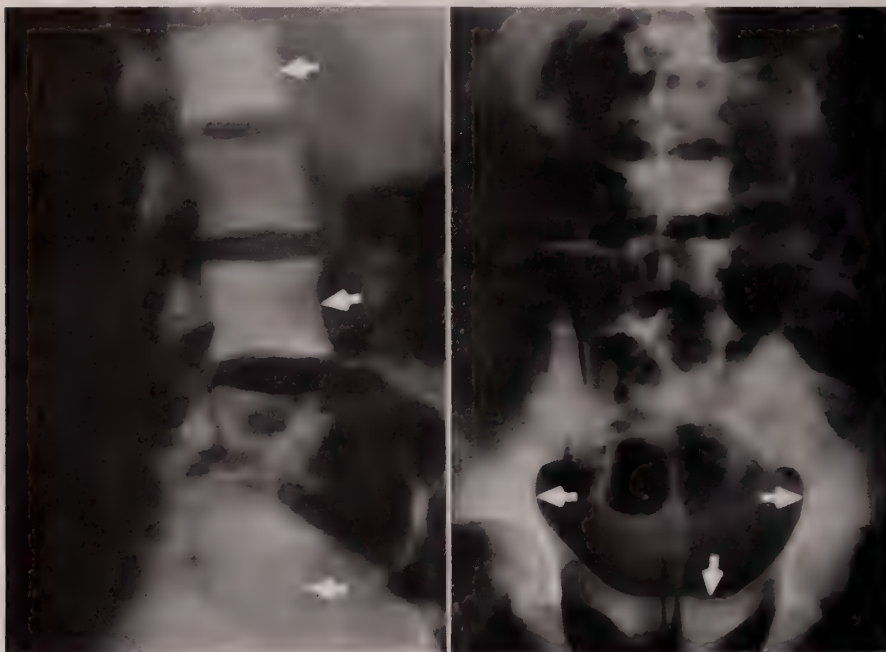
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CASE NO. 182

A 39 year old male was admitted to the hospital because of anorexia, abdominal pain and marked weight loss of six weeks' duration. Six years before his last admission, the patient underwent a subtotal gastrectomy for a bleeding gastric ulcer. This was performed in another institution and the pathological description of the specimen is unavailable. The patient was well until six weeks before admission, when he noted the onset of epigastric pain and fullness unrelieved by

the usual ulcer regimen. Three weeks prior to admission, the patient had two small episodes of hematemesis followed by melena. Because of the persistence of these signs and symptoms, hospitalization was advised.

An upper gastrointestinal tract examination was performed upon admission which revealed a normal esophagus. There was minimal delay to the passage of liquid barium at the cardia, and a 12 mm barium pellet was obstructed at the



Case 182, Fig. 1. Lateral view of the lumbar spine reveals the bodies of the 1st, 3rd and 5th vertebrae (arrows) to be densely sclerotic, with coarsened and distorted trabeculae, largely replaced by a homogeneous and dense matrix. This gives the appearance of "ivory vertebrae." The other vertebrae are similarly but less extensively involved.

Case 182, Fig. 2. The bony pelvis is extensively involved by a similar osteosclerotic process (arrows). The lumbosacral spine is also noted to be affected in this view.

esophagogastric junction. A subtotal gastric resection was noted. The gastric pouch was rigid and there was evidence of mucosal alterations and nodularities. There was a large exogastric mass which extended from the cardia to and around the gastrojejunostomy stoma. This anastomosis appeared to be narrowed but no discrete ulcerations were identified either on the gastric or jejunal sides of the stoma. The stomach contents emptied quickly into the jejunum and the visualized loops of small intestine appeared to be intrinsically normal.

Because sclerotic changes were noted in the lumbar vertebral bodies on the gastrointestinal series, a lumbosacral spine and pelvic examination was performed. This revealed the vertebral bodies of the 1st, 3rd and 5th segments of the

lumbar spine to be densely sclerotic in appearance. The trabeculae were coarse and distorted and largely replaced by a relatively homogeneous and dense matrix (Fig. 1). This produced an "ivory vertebra" appearance. The remaining lumbar vertebral bodies were similarly, but less extensively replaced by an osteoplastic process. There was no evidence of vertebral collapse, and the size of the vertebral bodies remained normal. The corresponding pedicles were also sclerotic, but again without thickening of the cortical margins or increase in size. The sacrum and almost the entire bony pelvis were similarly and extensively replaced by the osteosclerotic process (Fig. 2). No discrete lytic areas of bony destruction were identified.

Because of the involvement of the stomach both intrinsically and by an exogastric mass, gastroscopy was performed. The folds were noted to be reddened and friable. The rugae were thickened throughout and several nodules were noted as flat, whitish areas with necrotic centers. Biopsy was not performed, but the impression was that the stomach was involved by an infiltrative neoplastic process.

Laboratory examination revealed a persistent leukopenia of around 2000 white blood cells with a marked shift to the left. The hemoglobin was 10 grams per cent. Stool guaiac examinations were persistently positive. Bone marrow aspiration revealed clumps of signet-ring carcinoma cells which were consistent with a gastrointestinal tract origin. Alkaline phosphatase was 61 King-Armstrong units, acid phosphatase was normal.

DISCUSSION

The presence of widespread sclerotic lesions in bone suggests metastatic involvement. In females, the most common primary site is carcinoma of the breast; in males, carcinoma of the prostate. Often in these instances, the bone metastases are of a mixed lytic and blastic type. The extent of involvement is often considerable although solitary metastases may occur. Generalized lymphomas, especially Hodgkin's disease, can produce either localized or widespread osteoblastic changes in the skeleton. The presence of "ivory vertebrae" is typical in Hodgkin's disease with diffuse replacement of the normal bony trabeculae. Paget's disease can usually be easily differentiated from neoplastic disease by the presence of thickened and distorted bony trabeculae, widened cortical borders and increase in the overall size of the affected bones.

On rare occasions, other primary carcinomas have been noted to produce osteoblastic bone metastases. This is especially true when they are of a slow growing nature. The other primary sites of carcinoma causing sclerotic metastases are the urinary bladder, the gastrointestinal tract, the uterus and infrequently the lungs. Metastatic carcinoid tumors also tend to produce osteoblastic bony metastases.

Carcinomas of the stomach are the most common types of gastrointestinal tract neoplasms to metastasize to bone (1). In autopsy material, the incidence is usually 5 to 7 per cent of cases, (2, 3) and in series based on radiographic evidence alone between 2 and 4 per cent of cases (4). The bone lesions are usually

osteolytic in type but occasionally, as in the case described, present as osteoblastic metastases (3, 5). In most instances, the axial skeleton is primarily affected, possibly via the vertebral venous plexus of Batson. A few cases have been described in which the bone metastases produced the presenting symptoms in patients with carcinoma of the gastrointestinal tract (6).

Case Report: DIFFUSE OSTEOLASTIC METASTASES FROM CARCINOMA OF THE STOMACH.

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CASE NO. 183

A 39 year old female was referred for gastrointestinal x-rays as part of a routine physical examination.

Twelve years previously, the patient was admitted to the hospital following a three week history of crampy abdominal pain localized to the right lower quadrant. The pain had varied in intensity until three days prior to admission when it increased in severity and became associated with diarrhea and bloody stools.

Physical examination revealed a tender, ill-defined right lower quadrant mass. Sigmoidoscopic examination to 25 cm was negative, except for the presence of purplish-red blood. The abdomen was moderately distended and bowel sounds were increased and of high pitch.

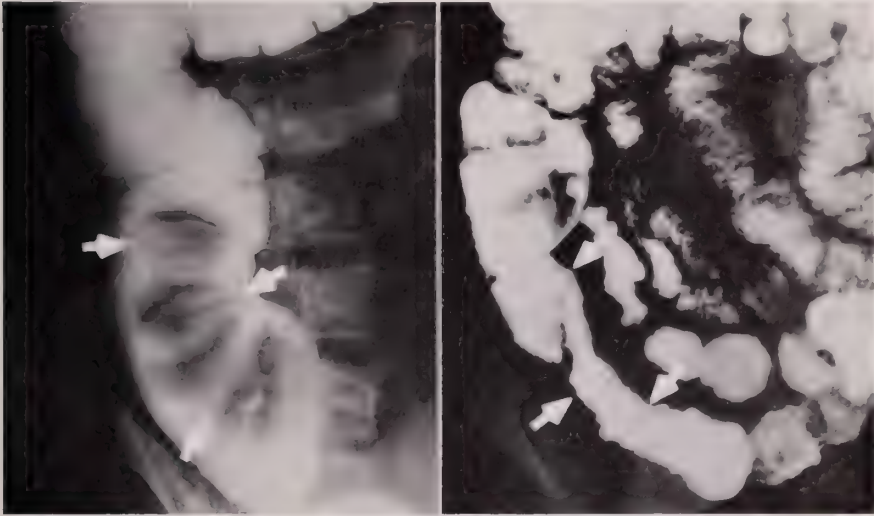
Barium enema examination revealed a large lobulated filling defect which occupied the cecum and proximal ascending colon (Fig. 1). The cecum was in normal location. No reflux into the terminal ileum occurred. Widely distended loops of small bowel were noted. The diagnosis of ileo-ileocolic intussusception with proximal small bowel obstruction was advanced. No attempt was made to reduce the intussusception with hydrostatic pressure.

At laparotomy, the intussusception was identified and reduced with moderate difficulty by traction upon the ileum. After reduction it was noted that a finger-sized tumor mass was present ten inches proximal to the ileocecal valve. Some thrombosed mesenteric veins were seen. Because of the partial compromise of the circulation and the size of the tumor, a resection was performed which included approximately six inches of bowel on either side of the tumor. The circulation of the bowel appeared intact after anastomosis. The postoperative course was uneventful.

The pathologist reported a specimen of small intestine measuring 25 cm in

length. The tumor measured 4x3x3 cm and was located near the center of the specimen. It was freely movable on a broad pedicle but the lumen of the bowel was almost completely occluded. The distal half of the tumor was necrotic. Superficial ulceration was present in the mucosa of the bowel distal to the tumor and the serosal surface of the bowel proximal to the tumor was darker than the rest of the specimen. The tumor was classified as a pedunculated fibroma, histologically benign.

When seen twelve years after her operation, the patient stated that she had been in excellent health throughout the intervening years and reaffirmed the fact



Case 183, Fig. 1. Barium enema examination demonstrates a large lobulated filling defect in the cecum and ascending colon (between arrows) which represents the intussusceptum. The cecum is in normal location. No reflux occurs into the terminal ileum. Widely dilated loops of small bowel are also seen.

Case 183, Fig. 2. Small bowel examination demonstrates an amorphous surface pattern in the terminal ten inches of ileum (between arrows). The contours are scalloped. Separation of this segment from an adjacent loop of bowel is apparent.

that her visit to the doctor was a matter of routine. She denied diarrhea, constipation, bloody stool, nausea, vomiting, abdominal pain and fever.

Barium enema and barium meal examinations revealed abnormal findings limited to the terminal 10 inches of ileum (Fig. 2). In this segment, the mucosal pattern was amorphous throughout. Although the bowel distended, distensibility was not uniform and the contours were scalloped. Some separation between this segment and an adjacent bowel loop was evident. Discrete ulcerations or fistulae were not present.

DISCUSSION

In considering the problem of small bowel infarction, a spectrum of cases emerges in which both the extent and the degree of bowel involvement vary

greatly. When major vascular deprivation occurs, all or most of the bowel is involved with irreversible gangrene. With more localized and less severe vascular compromise, merely a short segment of bowel may be involved, and this with only partial devitalization of its wall. It has been pointed out that the mucosa of the bowel is most sensitive to oxygen lack, followed by the muscular fibers and then the connective tissue. It follows, then, that differential infarction of a loop of bowel may occur in which the vascular insult results in limited necrosis of mucosal and muscular tissue, but which is insufficient to produce complete infarction of the bowel wall (1). Healing may then occur with organization, fibrosis, and limited mucosal regeneration.

Such a reconstituted loop of bowel may exhibit a variety of radiographic appearances depending on the extent of the histopathological changes (1, 2). When extensive scarring occurs, a benign stricture will be produced with obstruction and dilatation of the proximal bowel. With only mild fibrotic changes in the wall and atrophic mucosa, the radiographic findings in the case presented will appear. These include an amorphous surface pattern related to the atrophic mucosa, non-uniform distensibility related to the mild fibrosis, and separation from the adjacent bowel loops due to thickening of the wall and mesentery. Narrowing of the lumen sufficient to produce significant obstruction need not occur.

There are various causes of vascular deprivation which should be noted. These include idiopathic mesenteric venous or arterial thrombosis, arterial embolization, arteriosclerotic occlusion, diminished splanchnic blood flow secondary to cardiac failure (often with pre-existing arteriosclerotic vessels and possibly with reflex vasoconstriction in the splanchnic bed), (3, 4) and extrinsic compromise of the blood supply. This latter group includes all varieties of mechanical bowel obstruction such as intussusception, as in the case presented. The surgeon must be alert to the possibility of differential infarction and must not rely solely on the color of the bowel and arterial pulsations in determining when and how much bowel to resect. Furthermore, since secondary infection of the bowel wall will always play a role in the ultimate extent of the damage, judicious use of antibiotics is indicated.

The differential diagnosis in a case exhibiting mild changes is primarily with regional enteritis. As the pathological findings are similar, (5) so, too, are the radiographic appearances. A detailed and well documented history is often critical. Confusion with neoplasm should not occur.

Case Report: SEGMENTAL INFARCTION OF THE TERMINAL ILEUM SECONDARY TO INTUSSUSCEPTION.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Alfred S. Moscarella and A. Z. Freudenheim, Good Samaritan Hospital, Suffern, New York.

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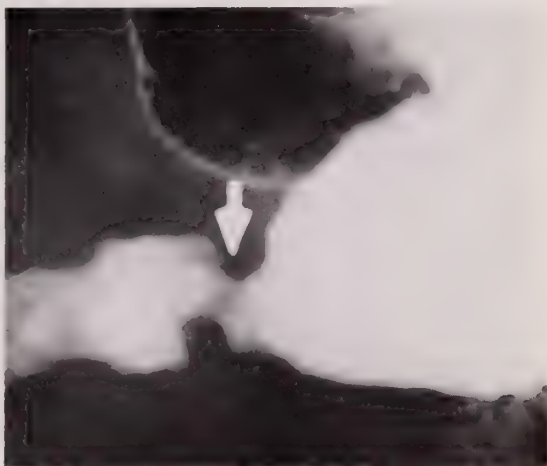
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CASE NO. 184

A 75 year old male was admitted in collapse following massive hematemesis and melena. Past history revealed hypertension with blood pressure ranging about 170/110. The patient denied previous gastrointestinal symptoms. The present illness started suddenly with nausea and was followed by vomiting of dark blood and passage of voluminous tarry stools. There was no pain. Profound weakness ensued.

On admission, the blood pressure was 130/76, pulse 92 and thready, and

Case 184, Fig. 1. The pyloric antrum and the base of the duodenal bulb are markedly narrowed (arrow). A definite ulcer crater is not seen.

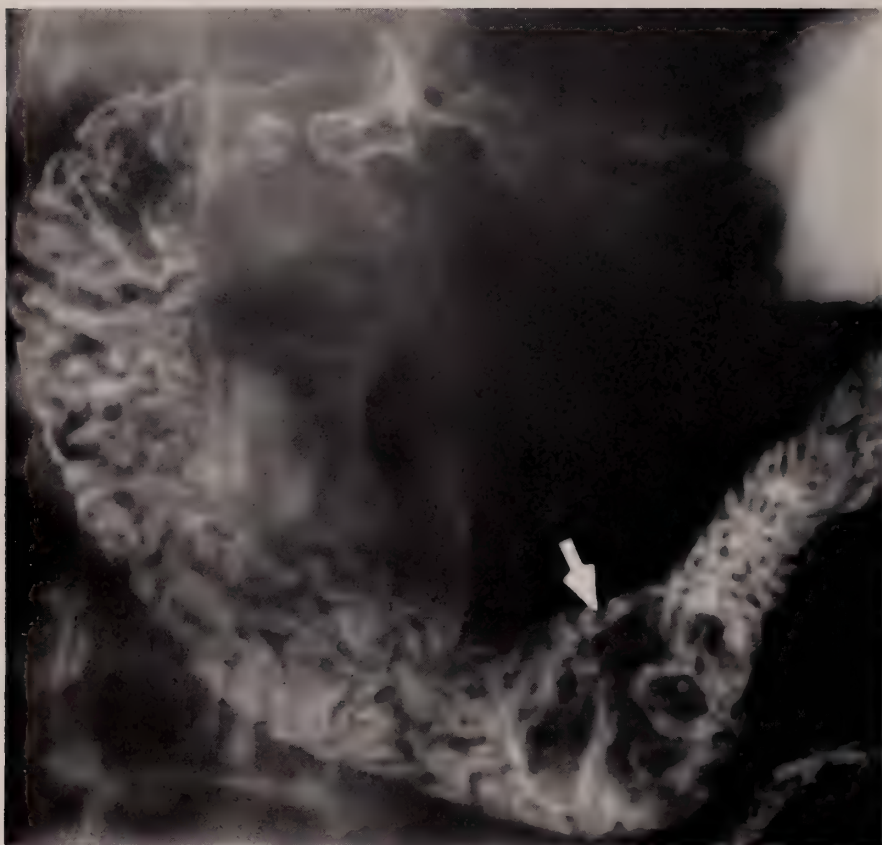


respirations 24 and labored. Physical examination was otherwise within normal limits. The patient received 5 units of whole blood and one unit of packed red blood cells over the next 18 hours. The blood pressure rose but the hemoglobin remained less than 8 Gm.

Barium meal examination was performed 18 hours after admission. There was a small direct hiatus hernia. The pyloric antrum and the base of the duodenal bulb were narrowed with thickened folds, but a definite ulcer crater was not seen (Fig. 1). In the third portion of the duodenum, an ovoid 4 cm filling defect was noted (Fig. 2). The defect was multilobulated and sharply outlined. The bowel lumen was slightly widened but there was no obstruction. An ulceration was not identified. In order to exclude the possibility of an unusual blood clot, films were made thirty minutes later which revealed no change in the findings.

The patient continued to bleed briskly and abdominal exploration was performed 12 hours later. The duodenum was deformed and the pyloric canal was markedly thickened. The stomach and duodenum were filled with blood. Ex-

ternal palpation of the third portion of the duodenum failed to reveal a mass. A subtotal gastrectomy was performed. Examination of the specimen in the operating room revealed a pin-point mucosal depression in the deformed pyloric canal. Although the appearance was consistent with that of a tiny ulceration, the surgeon did not feel that this lesion was the cause of massive bleeding. The



Case 184, Fig. 2. An ovoid filling defect is noted in the third portion of the duodenum (arrow). The defect is multilobulated and sharply outlined. The bowel lumen is slightly widened but there is no obstruction. There is no ulceration.

palpating finger was then introduced through the duodenal stump and a polypoid lesion of the third portion of the duodenum was identified. Resection of the third portion of the duodenum was performed with end-to-end anastomosis, followed by an antecolic gastrojejunostomy. The patient had a stormy post-operative course and expired on the third postoperative day. No autopsy was performed.

The pathologist (Dr. Robert T. Bryan) reported thickening and fibrosis of the pyloric antrum but no ulceration. The duodenal specimen contained a 4.5

cm lobulated neoplasm which had a broad base and a short stalk. There was no gross infiltration or ulceration. Microscopically, the neoplasm was adenomatous in structure, and although cellular atypism was noted, there was no frank carcinomatous change or infiltration. The stalk was clear and the basement membrane was intact. A number of hemorrhagic zones in the stroma of the tumor satisfactorily accounted for clinical bleeding. The diagnosis was benign adenomatous polyp of the duodenum.

DISCUSSION

Benign polypoid lesions of the proximal duodenum are relatively common; adenoma heads the list in frequency, composed either of Brunner's or mucous glands. In the infrapapillary portion of the duodenum, however, benign polypoid lesions are rare. Such lesions include adenoma, leiomyoma, fibroma, lipoma, angioma, neurogenic tumor and pancreatic rest (1, 2). The order of relative frequency is difficult to determine because of an inadequate number of cases reported, but it would appear that leiomyoma is most common, followed by pancreatic rest and adenoma.

Radiographic diagnosis rests initially on whether the lesion is mucosal or submucosal in origin. In the case presented, the polypoid configuration with sharp outlines is virtually diagnostic of a mucosal lesion, and all submucosal lesions may be excluded from consideration with the exception of a cavernous hemangioma (3). In the absence of signs of malignancy such as fixation, ulceration and narrowing, the diagnosis of adenoma should be advanced as a first choice. Unrecognized malignant degeneration may be present, but the frequency of this change does not approach that which occurs in colonic adenomata (4).

Aside from malignant degeneration, the common complications of adenoma include acute obstruction due to intussusception, chronic obstruction due to bulky size, and hemorrhage. While hemorrhage is a common occurrence, massive hemorrhage as in the case presented is rare.

Case Report: POLYPOID ADENOMA OF THE THIRD PORTION OF THE DUODENUM WITH MASSIVE HEMORRHAGE.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Henry J. Kaplan, Sheldon B. Adler, and A. Z. Freudenheim, Good Samaritan Hospital, Suffern, New York.

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Abstracts

Papers Presented before the Research Club of The Mount Sinai Hospital New York, N. Y.

A Comparison of the Hemodynamic Effects of the Closed and Open-Chest Methods of Cardiac Resuscitation in Normal Dogs and in Those with Acute Myocardial Infarction. Frank M. Weiser, M.D., Lawrence N. Adler, M.D., and Leslie A. Kuhn, M.D.

Experiments were conducted to compare, under controlled conditions, the hemodynamic effects of open and closed-chest cardiac compression in normal dogs and in those with acute myocardial infarction.

Cardiac outputs (dye-dilution method), central aortic, systolic, diastolic and mean pressures were recorded prior to electrically induced ventricular fibrillation and during fibrillation while closed and then open-chest cardiac compression was in progress in the same animal. Twelve normal dogs and ten with acute myocardial infarction, induced by plastic sphere coronary artery embolization, were studied in this manner.

The results indicate that the open-chest method generally provides greater cardiac output (averaging 61% of control values), and greater aortic, systolic, diastolic and mean pressures (48% of control mean aortic pressure) than the closed-chest technic (averaging 20% and 21% respectively), in both groups of animals. However, higher cardiac outputs were obtained with closed-chest massage in smaller dogs than in larger ones (39% vs 13% of control values), but even with small dogs, the cardiac outputs with closed-chest compression were less than with open-chest cardiac compression. Systolic ejection period and stroke volume were considerably diminished with the closed technic and, therefore, a rapid rate of compression (120/minute) was more effective than slower rates. With direct heart compression rates of 30-60/min were most efficacious.

The administration of epinephrine during massage with either technic, resulted in increased values of systolic, diastolic and mean aortic pressures.

It is concluded that under ideal conditions, permitting a choice of cardiac resuscitation technic, the direct open-chest method of cardiac compression produces hemodynamic responses more nearly approaching the normal state in the day, than the closed-chest technic.

Effect of Acutely Induced Hyponatremia on the Concentrating Mechanism of Normal Dogs. Berney Goodman, M.D., Jay A. Cohen, M.D., Melvin H. Kahn, M.D., and Marvin F. Levitt, M.D.

Experiments were designed to study the effect of an acute salt-retaining stimulus on the concentrating mechanism of maximally hydropenic dogs. In

control animals hypertonic mannitol infusions were administered at increasing rates. During such solute diureses two types of curves were obtained when T_cH_2O was plotted against CO_{sm} despite comparable initial maximum UO_{sm} : 1) T_cH_2O continued to rise between CO_{sm} s of 4 and 10 ml/min without a tendency to decline in slope at a CO_{sm} of 15 ml/min.; 2) T_cH_2O did not rise appreciably between CO_{sm} s of 4 and 10 ml/min with a tendency to decline in slope towards urinary hypotonicity at a CO_{sm} of 15 ml/min. The first type of curve was reproducible after discontinuing the infusion, returning to control CO_{sm} , and reinfusing the same solutions. The second type of curve was not similarly reproducible. Consequently only animals exhibiting type 1 T_cH_2O curves were studied. When phlebotomy of 300 cc or a prolonged mannitol infusion caused salt excretion to fall appreciably before the second diuresis, subsequent mannitol infusion revealed T_cH_2O curves which rose more slowly and stabilized at significantly lower levels without a tendency towards urinary hypotonicity. Diminished GFR was not consistently evident. These data suggest that the diminished T_cH_2O levels obtained after acute reduction in salt excretion may result from diminished distal tubular sodium supply secondary to enhanced proximal sodium reabsorption and/or reduced filtration rate.

Influence of Chemical Structure of Fatty Acids on In Vitro Esterification by Intestinal Mucosa. Alvin Gelb, M.D., and Jacques Kessler, M.D.

Other workers have established that esterification of palmitic acid by slices of small intestine occurs *in vitro* in Krebs Ringer solution, and is promoted by the addition of bile salts and albumin. This experiment was designed to study the influence of chain length and degree of unsaturation of the fatty acid on this system. Slices of hamster proximal small intestine were incubated for 30 minutes in a solution of Krebs Ringer, sodium taurocholate and albumin, to which 170–180 millimicromoles of C-14 labelled fatty acid had been added. Lipids were extracted and nonesterified lipids were removed. Aliquots were counted in a thin window Geiger Muller Counter. Results were expressed as percent esterification per 100 mg of tissue for each fatty acid. Results indicate that for saturated fatty acids, degree of esterification differs for each, maximum esterification occurring with myristic acid, 14 carbons. Percent esterification decreases as the chain length either increases or decreases from 14 carbons, so that fatty acids with 10 carbons or fewer are only slightly esterified. As the degree of unsaturation increases, the percent esterification decreases also in stepwise fashion. These results indicate that at least *in vitro* the small bowel differentiates between fatty acids in an orderly manner depending upon chain length and degree of unsaturation.

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PATTERNS OF BONE CHANGE IN THE MALIGNANT LYMPHOMAS¹

JOHN E. MOSELEY, M.D.

New York, N.Y.

The classification of malignant disorders arising primarily in lymph nodes or other lymphoid tissue has long been a subject of much controversy. Willis (1) considers that the basic cells of all forms of lymphoid tumors are derived by divergent differentiation from primitive mesenchymal stem cells and that the lymphomas they give rise to are therefore related variants of one disease. He believes that the nomenclature applied to the principal variants has descriptive and clinical value but should not be construed to denote distinct pathologic entities.

Some authors have chosen to include all these conditions under the noncommittal designation "conditions primarily affecting lymph nodes." More often they have been grouped together as the "malignant lymphomas." This designation is used with full recognition of the fact that there is no complete agreement that Hodgkin's disease is a neoplasm. With that understanding the malignant lymphomas may be considered to include Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and giant follicle lymphoma.

HODGKIN'S DISEASE

Hodgkin's disease may occur in any one of the three basic forms defined by Jackson and Parker (2). Hodgkin's *paragranuloma*, essentially a disease of the lymph glands, is usually primary in the cervical lymph nodes, only very slowly progressive and has an excellent five year survival rate. Histologically the affected nodes show a diffuse infiltration by adult lymphocytes. Scattered within the mass of lymphocytes are typical Reed-Sternberg cells which are the cytologic hallmarks of Hodgkin's disease in all of its forms. Reticulum cells are present in varying numbers. The pathologic process does not invade the capsule. There is no necrosis or fibrosis and eosinophilia is not marked. This form of the condition comprises approximately eight or nine per cent of all cases of Hodgkin's disease. Hodgkin's *granuloma*, which represents the vast majority of all cases, may involve isolated groups of nodes or may be widespread. Some cases have been reported in which the disease was confined to a single organ with no lymph node involvement (3). In addition to involvement of the superficial lymph nodes there is frequent involvement of the less apparent internal lymph glands particularly the retroperitoneal and para-aortic nodes. The histologic appearance of Hodgkin's granuloma is characterized by the presence of Reed-Sternberg cells and marked pleomorphism. Lymphocytes are numerous and plasma cells are usually

¹ From the Department of Radiology, The Mount Sinai Hospital, New York 29, N.Y.

seen. The presence of eosinophils is considered one of the most outstanding features of this common disorder. Necrosis and fibrosis are also characteristic and the pathologic process may extend into the capsule. The prognosis in Hodgkin's granuloma is extremely variable. Cases with essentially the same histologic appearance may live for 15 years or more or may die a few months after diagnosis. Hodgkin's *sarcoma*, which is usually primary in the retroperitoneal nodes, is a characteristically invasive and destructive process with a very poor prognosis. Histologically the lesions consist of large numbers of cells, two or three times the size of normal lymphocytes. These are considered by Jackson and Parker (2) to be extremely anaplastic forms of Reed-Sternberg cells. More typical Reed-Sternberg cells are also present associated with scattered lymphocytes and reticulum cells. Eosinophils are rare. Necrosis is frequent. The capsule may be extensively invaded and the adjacent tissue involved. This form of the disease is rapidly progressive, most patients dying within a year and a half after diagnosis. Practically none survive for five years.

It is clearly recognized that the Jackson-Parker subgroups of Hodgkin's disease may undergo transformation from one type to another. That is to say, some cases of Hodgkin's paraganuloma may, after varying periods of time, become transformed into Hodgkin's granuloma and Hodgkin's granuloma may become transformed into Hodgkin's sarcoma with corresponding changes in prognosis. While practically all patients with Hodgkin's paraganuloma survive for more than five years and practically all of those with Hodgkin's sarcoma die within this period, in the granuloma group, which comprises about ninety per cent of all patients with Hodgkin's disease, histological appearance has no prognostic value. Jelliffe and Thomson (4) contend that a useful index of prognosis in this condition is the stage of the disease when first seen. According to their system, cases are designated Stage I when there is lymph node involvement in only one lymph node chain, Stage II when the disease is confined to two or more adjacent chains in either the upper or lower half of the body and Stage III when there is generalized lymph node involvement, constitutional manifestations for which no other reasonable cause can be found, involvement limited to the retroperitoneal lymph glands or involvement of structures other than lymphatic. These British authors found that cases classed as Stage I or II had a five-year survival rate of approximately fifty per cent while those classed as Stage III very rarely survived that long.

Bone Lesions in Hodgkin's Disease

It is generally considered that in practically all cases of Hodgkin's disease in which the pathologic process has run its full clinical course, some degree of bone involvement will be found on careful and extensive necropsy investigation of the skeleton. At least some miliary seeding of the marrow of some bones will be found (5). The disease may be widespread throughout the marrow without causing sufficient spongiosal or cortical destruction to produce lesions demonstrable by roentgen examination.

The incidence of radiographically demonstrable bone lesions in this disease,

however, is another matter. Published reports show variations in the incidence between 7.5 and 26 per cent. Analysis of the larger series (6-10) would suggest an incidence of approximately 14 per cent (Table I). In spite of the formidable number of reported cases in Table I, however, we have the distinct impression that an incidence of 14 or 15 per cent is much too low. If one has a special interest in bone lesions and makes a thorough and periodic search for them in each case of Hodgkin's disease observed he is apt to gain a similar impression. It is another thing entirely to review the records of a number of cases in many of which, for various reasons, the skeletal system has been inadequately studied or not studied at all. In such a review, one will find cases in which symptoms possibly referable to a bone lesion apparently have been considered part of the general constitutional manifestations of the disease, and others in which a symptomatic area having been subjected to roentgen examination once with negative results has not been followed by repeat examinations despite the known tendency for pain to precede demonstrable bone pathology in many instances.

TABLE I

Incidence of Demonstrable Bone Involvement in Hodgkin's Disease as Reported in Several Large Series

	Cases Reported	Cases with Bone Involvement	Incidence of Bone Involvement (%)
Craver and Copeland (6)	172	27	15.7
Dresser and Spencer (7)	149	16	10.7
Fucilla and Hamann (8)	94	11	11.7
Fisher, Kendall and Van Leuven (9)	154	25	16.1
Vieta, Friedell and Craver (10)	257	38	14.8
Total:	826	117	14.2

Demonstrable lesions may occur at any time during the course of the disease. While some patients may survive for many years following the discovery of an osseous lesion, it is noteworthy that of 25 patients with skeletal involvement reported by Fisher *et al.* (9) twenty of them died within two years after the demonstration of the first bone lesion.

Occasionally attention is first drawn to the presence of Hodgkin's disease by symptoms or signs resulting from some form of bone involvement. Pain is the most common complaint and in some instances where a more accessible portion of the skeleton is affected there may be tenderness and some swelling. *Localized pain may be present for months before the lesion can be demonstrated radiographically.* On the other hand, some large lesions may be completely silent and may be discovered purely by chance. Neurologic deficits due to extension of the lesion into the spinal canal may be the first manifestation of vertebral involvement and sciatica-like pain may signal the presence of large retroperitoneal pelvic masses.

Skeletal lesions may develop as a result of 1.) hematogenous spread; 2.) direct

invasion from contiguous diseased lymph nodes or 3.) it is possible that they may arise *de novo* in the marrow. There have been a few reports of cases in which lesions with the histologic appearance of Hodgkin's disease have been limited to the skeleton for two or three years without any evidence whatever of involvement of the nonosseous tissues. That deep inaccessible nodes may have been primarily involved in such cases remains a possibility, however.

Bone lesions may be multiple or solitary. According to Vieta *et al.* (10) in 65 per cent of cases with osseous involvement, lesions may be demonstrated in more than one bone. Fisher and his associates (9) found multiple bone involvement in 14 of 25 patients (56%). The central segments of the skeleton are most frequently affected. *The spine is by far the most common site of involvement.* The great majority of lesions are found in the lower dorsal and upper lumbar vertebrae, especially the latter. Cervical and upper dorsal vertebrae, however, may also be affected. The pelvis is also commonly affected and here there is a predilection for the wings of the ilia, usually adjacent to the sacro-iliac joints. The ribs, femora and sternum are next in order of frequency. The clavicles and skull are not uncommonly involved but the fact is that practically any bone may be the site of a Hodgkin's lesion.

In considering the diagnosis of a bone lesion with features consistent with Hodgkin's disease it is important for the young radiologist to keep in mind the fact that a significant number of cases of Hodgkin's disease do not show radiographic evidence of mediastinal or hilar adenopathy. This reminder is not necessary for the more experienced radiologist but it has often been possible to confuse a beginner at conference discussions by showing him the patient's normal chest film along with films showing destructive bone lesions. Pierce *et al.* (11) found no roentgen signs of intrathoracic abnormality in over one-third of 214 cases of Hodgkin's disease. More recently Fisher and associates (9) found no roentgen evidence of enlarged intrathoracic glands in 69 of 154 cases. In addition it may be helpful to remember that Hodgkin's disease and lymphosarcoma may present masses in the anterior mediastinum without involvement of the middle or posterior mediastinal nodes. This should be kept in mind when considering a destructive lesion of the sternum associated with a retrosternal mass or plaque of soft tissue without evidence of hilar or other mediastinal adenopathy. Furthermore, the variety of radiographic patterns which may occur in intrathoracic Hodgkin's disease, other than the more typical hilar and paratracheal adenopathy, is not always fully appreciated. Briefly, pulmonary Hodgkin's lesions may be 1.) *Lobar*. An entire lobe may be involved, the appearance being similar to that of bronchogenic carcinoma; 2.) *Miliary*. Diffusely scattered miliary nodules may resemble hematogenous tuberculosis or pulmonary sarcoidosis; 3.) *Nodular*. Large nodular densities limited to the lung parenchyma can develop without discernible evidence of mediastinal involvement. These may be impossible to differentiate from a number of other conditions, notably metastatic carcinoma and mycotic infections. (Fig. 1.) When seen with destructive bone lesions they are likely to suggest an immediate diagnosis of metastatic carcinoma if no enlightening clinical information is available. More confusing

is the fact that the nodules may on occasion undergo cavitation; 4.) *Lymphangitic*. Hodgkin's tissue may be confined to the perivascular and peribronchial lymphatics extending from the hilus into the lung parenchyma as linear infiltrations. Variations in the intrathoracic manifestations of Hodgkin's disease have been discussed and illustrated by several authors including Wolpaw *et al.* (12), Sheinmel *et al.* (13) Vieta and Craver (14) and Fried (15).



FIG. 1. Hodgkin's Disease. There are multiple nodular lesions scattered throughout both lungs. There is no evidence of mediastinal adenopathy. The parenchymal changes resemble metastatic disease.

When the lesions of Hodgkin's disease occur in bone their histologic appearance is essentially similar to that seen in the nonosseous tissues. Occasionally, however, the diagnostic features of the lesion may be obscured and distorted by necrosis and secondary inflammatory reaction. Both Jaffe (5) and Lichtenstein (16) have commented on the difficulty which may occasionally arise in making a specific pathologic diagnosis on tissue from bone lesions taken either by needle aspiration biopsy or by open operation. Hodgkin's tissue may be distributed in

the bone marrow as many small scattered areas of disease. These may or may not have destroyed the local bone trabeculae. As these foci enlarge the regional osseous tissue is destroyed. A large Hodgkin's focus will replace the normal bone structure and in some cases may invade the cortex. Hodgkin's tissue, however, may extend for some distance through a bone, destroying much of the trabecular structure and eroding the inner aspect of the cortex without actually perforating it. In some instances the pathologic process will provoke various degrees of *reactive* osteosis. The new bone may be laid down along the adjacent trabeculae, within the tumor mass or at the periphery of the lesion. This apparently occurs both in lesions which originate as hematogenous deposits or as a result of invasion from contiguous lymph nodes. When the lesions are unaccompanied by any reactive new bone they appear radiographically as areas of lucency (*osteolytic*). When new bone is intermingled with destructive Hodgkin's tissue there is a *mixed* osteolytic and osteoblastic appearance. When reactive osteosis is the dominant process the appearance is that of *osteosclerosis*. Peripheral bone reaction results in increased bone density at the border of the lesion.

The Spine

In all studies the spine has been found to be the most frequent skeletal site of Hodgkin's involvement. The vertebral body is involved and only rarely are the vertebral appendages affected. Not infrequently, however, lesions in the dorsal vertebrae are associated with involvement of the adjacent ribs. Usually vertebral lesions are multiple but involvement of a single vertebra is by no means rare. The majority of lesions are found in the lower dorsal and upper lumbar vertebrae, for the most part between the twelfth dorsal and fourth lumbar bodies. Some reports have indicated a greater incidence of involvement in the lower cervical and upper dorsal spine but this has not been so in our experience nor in that of most observers. Vertebral lesions may be osteolytic, mixed or sclerotic. We have found a substantial majority to be mixed. Of the others, sclerotic lesions outnumber those that are purely lytic. There have been conflicting reports regarding the relative frequency of these three types of lesions but it is probable that there has been some difference among the observers regarding the criteria for mixed and sclerotic lesions. In most cases where more than one vertebra is involved the lesions tend to be of the same type. The affected vertebrae may show various degrees of collapse but generally this is minimal or moderate (Figs. 2, 3). Major degrees of collapse, when seen, usually occur with predominantly lytic lesions. Where there is significant osteoblastic reaction collapse is more moderate and sclerotic (ivory) vertebrae tend to maintain their normal dimensions. In most instances the intervertebral disc space is characteristically spared or only slightly narrowed. In an occasional case, however, during the late stages, it may be practically obliterated (Fig. 4). Associated paravertebral soft tissue masses may be noted in some cases. Fisher *et al.* (9) found paravertebral soft tissue masses in slightly over one half of

dorsal spine lesions. Posterior mediastinal node involvement raising the pleural reflection can be seen in some cases with or without adjacent bone involvement.

The most important diagnostic feature of osseous Hodgkin's disease is erosion of the anterior margins of affected vertebral bodies. This is apparently due to the effect of pressure and invasion of the bone by adjacent diseased posterior mediastinal and para-aortic lymph nodes. In some cases the shadow of enlarged posterior mediastinal nodes adjacent to the erosions can be demonstrated by



FIG. 2. Hodgkin's Disease. There is a generalized sclerosis of the bodies of the twelfth dorsal and second lumbar vertebrae. The trabecular pattern of the bone has been lost. There is no collapse. The anterior margins of the vertebral bodies are intact.

bulging of the regional pleural reflection and by anterior displacement of the barium-filled esophagus. In the abdomen enlarged para-aortic nodes may cast the shadow of an abnormal mass anterior to the lumbar vertebrae in the lateral projection. In older patients a calcified abdominal aorta may be displaced anteriorly by such a mass. Less often para-aortic node enlargement can be demonstrated in the antero-posterior projection by obliteration of the normal shadow of the psoas border. The confusing fact is, however, that in many cases even when anterior marginal erosion of the vertebrae is advanced, no such soft tissue shadow can be demonstrated (Fig. 5). It is to be noted also that in some cases pathologic changes in the vertebral body *precede* evidence of marginal

erosion. Vertebral involvement, of course, may be unaccompanied by anterior marginal erosion during the entire course of the process and these lesions are considered to be metastatic in nature. Unfortunately, there is a paucity of information in the pathological literature regarding this very interesting problem. Recent developments in lymphangiography have provided a technique which holds much promise for the radiologic exploration of these pathologic processes.

When marginal erosion of a vertebral body occurs the process may be entirely osteolytic but more often it is associated with mixed or sclerotic changes in the

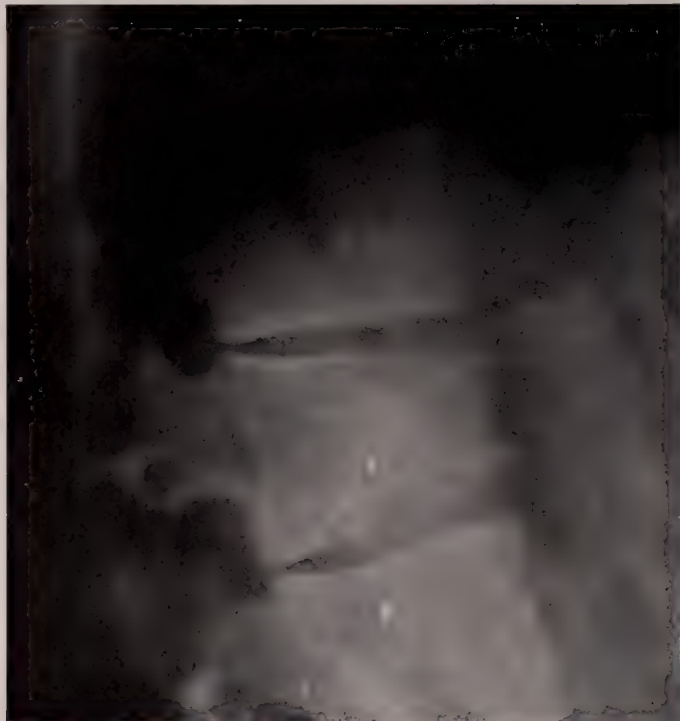


Fig. 3. Hodgkin's Disease. There are mixed lytic and blastic changes in the body of the first lumbar vertebra. The vertebral body has undergone moderate collapse. There were no demonstrable associated soft tissue masses.

adjacent bone. These changes may involve the entire vertebral body or only a portion of the bone adjacent to the area of destruction. As is the case with abdominal aneurysms the intervertebral discs resist the pressure or invasion of the enlarging mass so that the upper and lower portions of the vertebral bodies are destroyed to a much less extent than the center and this only in the more advanced stages of the process. Occasionally osteoblastic reaction can be noted within the tumor mass away from but adjacent to the involved vertebra. Sclerotic changes may begin as a coarsening of the trabeculae throughout the vertebral body (Fig. 6) or as a localized poorly defined patch of increased density (Fig. 7B). The rate of progression of this process no doubt varies but

a radiographically normal vertebra may develop into a dense "ivory" vertebra within months (Figs. 7, 8). Although few longitudinal studies of the spine in Hodgkin's disease have been reported, in at least some cases purely sclerotic



FIG. 4. Advanced Osseous Hodgkin's Disease. There are advanced mixed destructive and productive changes involving the lower dorsal and lumbar vertebrae. The anterior margins of all the vertebral bodies are invaded and destroyed by adjacent diseased lymph nodes. The upper and lower portions of the vertebrae are much less involved than the central portions of the bone. The intervertebral disc spaces are considerably narrowed. The twelfth dorsal body is partially collapsed. The patient was a 22 year old male in whom the disease started in 1947. Osseous involvement was first noted five years later. There were sclerotic changes in the pelvis involving the ilia especially in the region of the sacro-iliac joints and the femora and humeri were the sites of mixed lesions. Large retroperitoneal masses could be palpated and there was also diffuse involvement of the stomach by Hodgkin's disease. Death occurred three years after the onset of bone involvement.

changes may eventually give way to destruction and demonstrable osteolysis (9, 14).

The bone changes which may occur in Hodgkin's disease are frequently described as being nondescript but in the spine, which is the most frequent site of

involvement, this description would seem to us to be unjustified. Metastatic carcinoma and other diseases can be manifested as mixed or sclerotic lesions of the vertebrae but where there is anterior marginal erosion with or without demonstrable adjacent soft tissue masses, particularly in young patients, the prob-

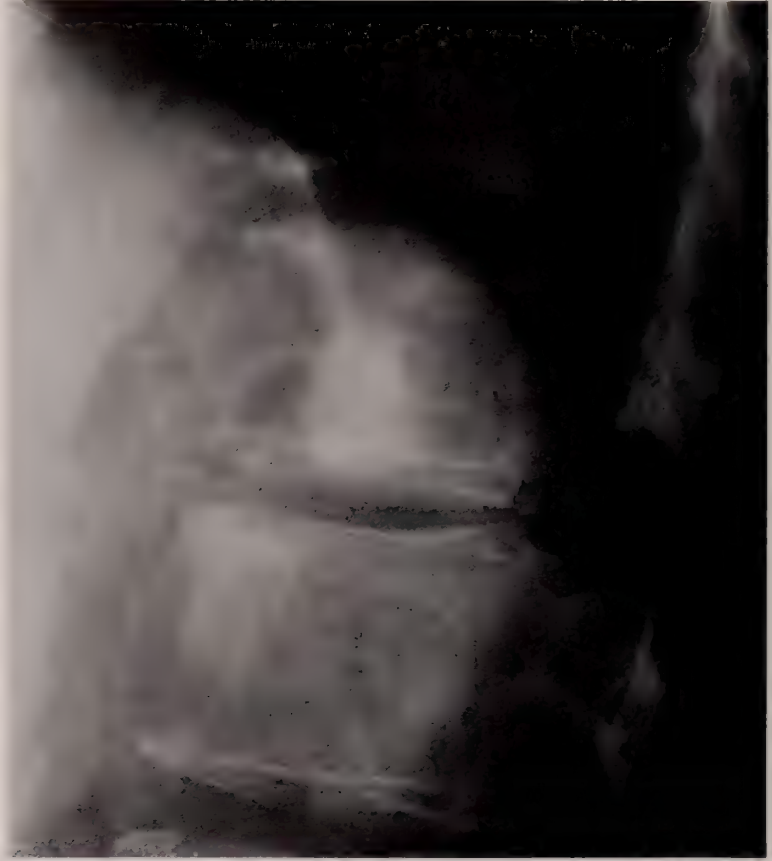


FIG. 5. Hodgkin's Disease. There is anterior marginal erosion of the body of the twelfth dorsal vertebra. At the margin of the invading lymphoma there is an osteoblastic reaction. The intervertebral discs and the upper and lower vertebral margins are spared. No regional soft tissue masses could be demonstrated radiographically. The patient was a 43 year old male who first noticed enlarged glands in his neck in 1956. The initial osseous manifestation occurred in 1958 when mixed changes were demonstrated in his sternum. The vertebral lesion was demonstrated in July 1960 two weeks after his first complaint of back pain. Death occurred in November of the same year.

ability of lymphoma is great. In older individuals, erosion due to aortic aneurysm is not apt to be associated with osteoblastic change in the vertebra and often some calcification can be demonstrated at the periphery of the aneurysm or there is dilatation of the calcified aorta at the level of the bone lesion. Calcification is not seen in the para-aortic or posterior mediastinal nodes of Hodgkin's disease unless there has been previous radiation therapy. Marginal erosion of the vertebrae may occur in lymphosarcoma and has been reported in a case of chronic

lymphatic leukemia (9) but it is rare, if it occurs at all, in association with carcinomatous nodes. Sclerotic vertebrae, of course, are common in Paget's disease. This condition, however, is likely to be seen in patients over forty years



FIG. 6A. Hodgkin's Disease. The body of the fourth lumbar vertebra is increased in density due to a coarsening of the bony trabeculae. There is no collapse and the intervertebral disc spaces above and below are normal.

of age. In addition, the trabeculae, if they can be seen, tend to be unusually coarse and vertically striated. In most cases the cortical bone is thickened as it is characteristically in other skeletal areas. Not infrequently there is a layer

of subcortical increased bone density which produces a double contour or "picture frame" appearance (17). Usually the Paget's vertebra is enlarged in its sagittal or coronal diameter. It must be recognized, however, that all degrees of sclerosis

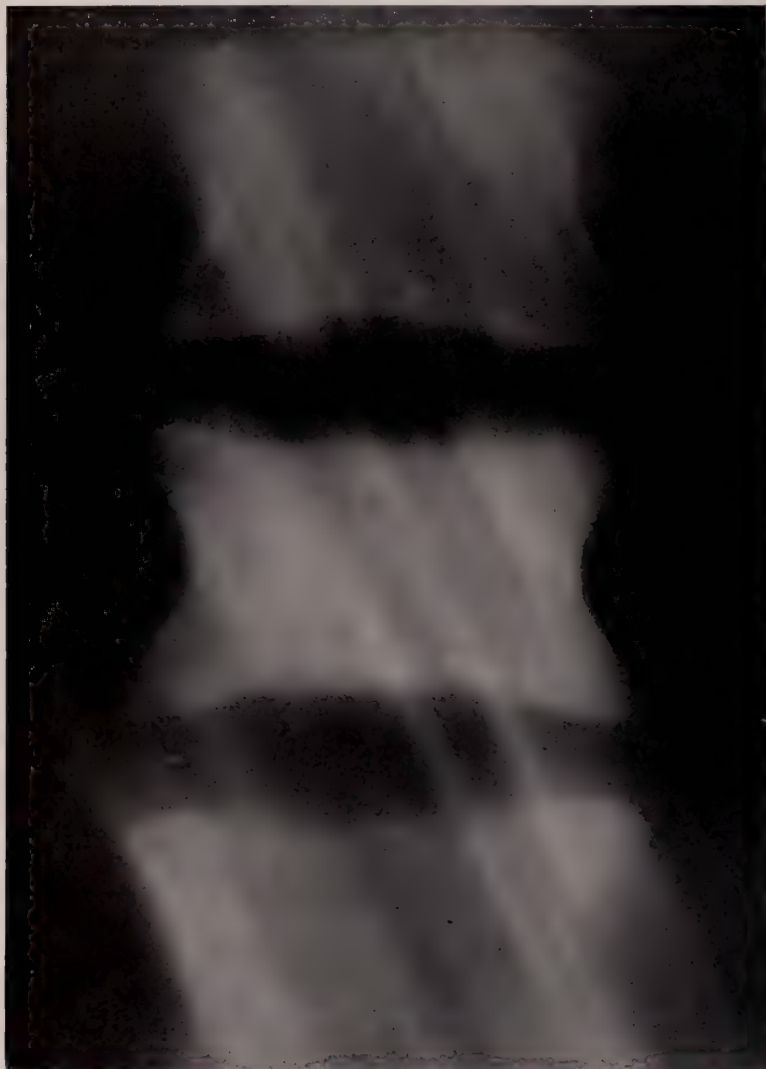


FIG. 6B. Tomography shows no lytic lesions. The increased density is due to coarsening of the trabeculae. This patient is a 21 year old female who first noticed an enlarged gland in her neck in April 1959. She first complained of back pain in June 1962 at which time this examination was made. At present her general condition is good.

can occur in metastatic disease and in other conditions so that when marginal erosion is not present the diagnostic possibilities are increased.

The Pelvis

In most reports involvement of the pelvis is exceeded in frequency only by involvement of the vertebral column. The lesions may be mixed, sclerotic or

lytic. We have found no predominance of any one of them and there is no agreement in the literature regarding the relative frequency of each type. We do consider, however, that sclerotic changes are more frequent in the spine and pelvis than in any of the other bones. While any part of the pelvis may be affected there is a predilection for the wings of the ilia, particularly *adjacent to the sacro-iliac joints* (Fig. 9). It is considered that lesions in the sacro-iliac regions are caused by invasion from adjacent diseased lymph glands of the iliac chains. Lymph node masses can sometimes be seen to obliterate the normal soft tissue shadows of the obturator internus and psoas muscles as they cross the pelvic

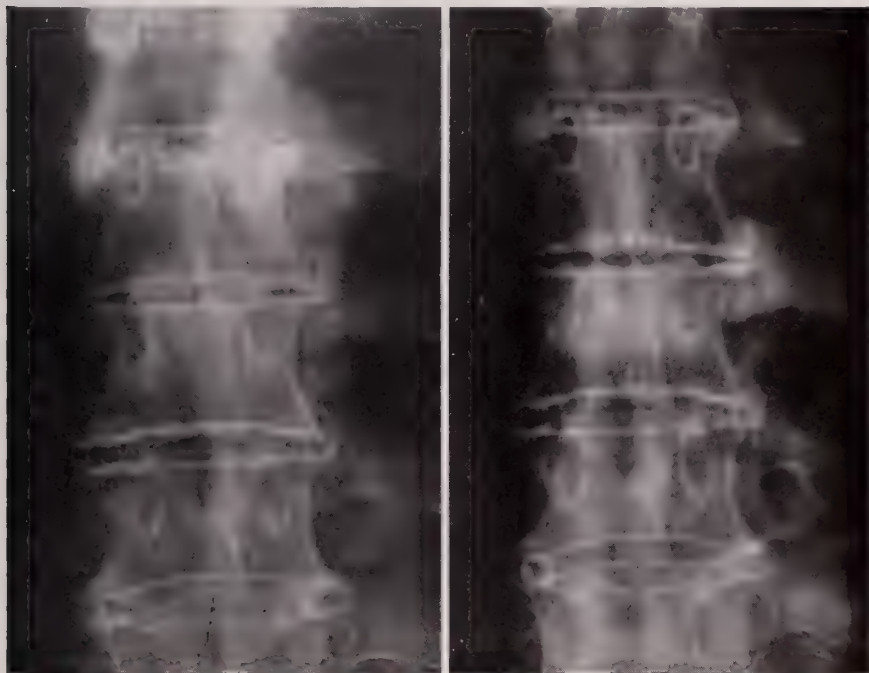


FIG. 7. Hodgkin's Disease. A.) Dorsal spine examined 11-22-58 because of back pain showed no osseous involvement. B.) Re-examination 8-14-59 showed a poorly defined area of sclerosis in the upper half of the body of the seventh dorsal vertebra.

cavity. Intravenous urography may aid in demonstrating these enlarged nodes by revealing displacements of the ureter at this level. Bizarre patterns of destruction may be seen in the pelvis. Osteolytic lesions may have a sclerotic border, or a poorly defined margin. They may also appear as poorly circumscribed areas of mottled destruction or as cystlike lesions. Sclerotic lesions may bear a striking resemblance to Paget's disease and poorly defined areas of sclerosis adjacent to the sacro-iliac joints resemble areas of stress sclerosis in some cases. Pelvic sclerotic lesions may also become transformed into mottled areas of mixed sclerosis and destruction (9). Evidence of destructive change can become apparent in such areas within a few months. Involvement of the ischial bone is not uncommon and all three basic types of lesions have been noted at this site (Fig. 9). Lytic lesions occurring in the pelvis are nonspecific and their etiology

is not likely to be suspected purely on the basis of their radiographic appearance (Fig. 10). On the other hand, sclerotic pelvic lesions from any cause are sufficiently uncommon in younger individuals to warrant suspicion of lymphoma when seen. Localization of such lesions to the ilium adjacent to the sacro-iliac articulations and demonstration of an associated soft tissue mass should increase the suspicion.

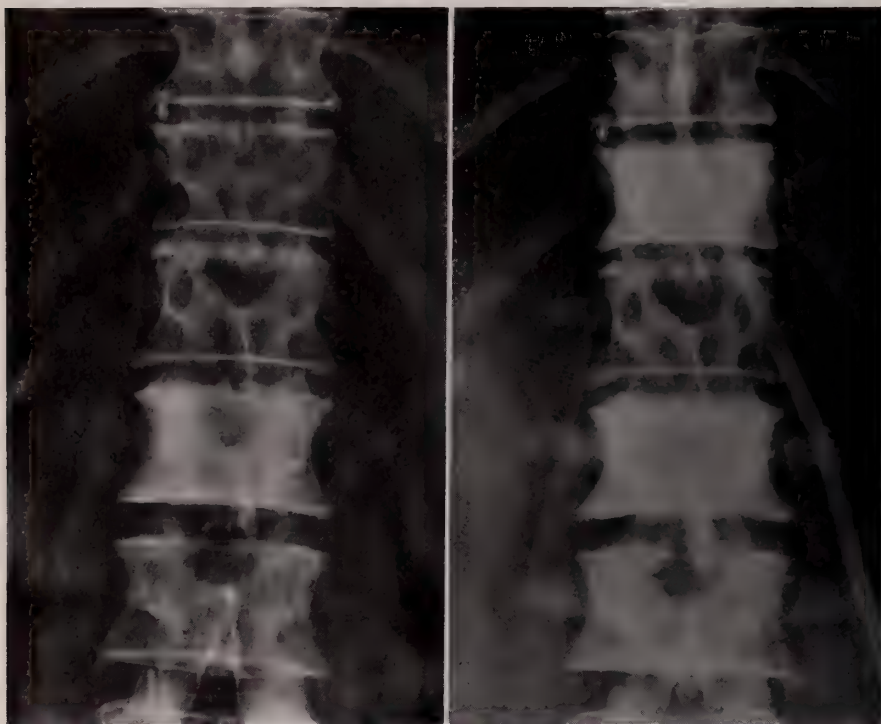


FIG. 8. Hodgkin's Disease. This is the same patient shown in Fig. 7. A.) Examination on 11-22-58 showed a sclerotic second lumbar vertebra. There was also some early coarsening of the trabeculae of L_3 . The twelfth dorsal vertebra was completely uninvolved. B.) Nine months later the twelfth dorsal vertebra is densely sclerotic and the changes in L_2 and L_3 have advanced.

The Ribs

The ribs are among the more frequently affected sites of bone involvement in Hodgkin's disease. Lytic lesions are most commonly found and mixed lesions may be seen occasionally but predominantly sclerotic involvement is unusual. There is nothing distinctive about the appearance of the affected ribs. Areas of lysis may be localized or more commonly long segments of the bone show a moth-eaten type of destruction. Destruction of the trabeculae with erosion of the inner margin of the cortex may be noted in some cases. Pathological fractures are not uncommon. In some segments of affected bone the cortex may be completely erased. In fact, whole segments of a severely involved rib may vanish. Occasionally a periosteal reaction develops adjacent to a diseased segment of

bone and, as in all lymphomas, this reaction is usually only moderate in degree. It is practically never lamellated and is not likely to be seen in the absence of a demonstrable underlying bone lesion. In some instances Hodgkin's lesions of the ribs may expand the bone (Fig. 11). Expansion may also occur with lesions of the sternum. Soft tissue mass formation may be associated with rib destruction and such masses can often be palpated on the chest wall. Rib involvement is sometimes associated with pleural effusion. On routine chest films such an effusion may obscure the underlying rib lesion. There is no doubt that in many cases rib involvement is secondary to Hodgkin's disease of the pleura. It should be remembered that pleural involvement may occur in this disease without any apparent involvement of the lung or intrathoracic lymph nodes. Ribs may be invaded from adjacent diseased pleura. There are many small collections of lymphoid cells in the pleura and pleural involvement with effusion in Hodgkin's disease is common. The effusion need not be secondary to pressure on lymphatic or blood vessels by enlarged mediastinal nodes. Occasionally an affected rib is incorporated in a large mass of lymphomatous tissue which involves not only the rib but the adjacent pleura and lung as well.

The Sternum

Sternal involvement in Hodgkin's disease is common. As a matter of fact, *Hodgkin's disease and myeloma deserve important consideration in the differential diagnosis of any non-traumatic destructive lesion of the sternum.* In myeloma the pathologic process is purely lytic with few exceptions. In Hodgkin's disease the lesions may be entirely lytic but an equal number or more show mixed osteolytic and osteoblastic changes (Fig. 12). The manubrium is the part usually affected. The pathologic process sometimes expands the bone and frequently perforates the cortex giving rise to a moderate periosteal reaction or, commonly, a soft tissue mass. In some instances osseous spicules develop within a soft tissue mass anterior to the involved sternum and assume a position perpendicular to the involved bone (Fig. 13). The result is a "sun-burst" appearance similar to that sometimes seen in osteogenic sarcoma. A similar pattern has been described in myelomatous involvement of the sternum (18). Usually a retrosternal soft tissue mass can be found associated with the sternal lesion. This may be a rounded or lobulated density convex posteriorly with the base toward the sternum. More often, however, there is a plaque of thickened soft tissue about .5 to 2 cm wide lying along the posterior margin of the sternum and parallel to it. This can be an important radiographic finding since *it may precede any other intrathoracic manifestation of Hodgkin's disease or any demonstrable lymphomatous involvement of the sternum.* It is often associated with *presternal edema.* This type of retrosternal infiltration, described in more detail by Fleischner *et al.* (19) possibly originates from the pleura, subpleural tissue or periosteum. It is not to be confused with large anterior mediastinal lymph nodes which may be seen in some cases of Hodgkin's disease. The anatomical relationships of the lymph vessels of the chest wall with extensive anastomosis between the subpleural, intermuscular and subcutaneous systems can easily account



FIG. 9. Hodgkin's Disease. There are poorly margined areas of sclerosis involving the iliac bone adjacent to the sacro-iliac joint and at its lateral margin. Sclerotic changes are also noted in the ischium. Frequently when there is sclerotic involvement of bone in the region of the sacro-iliac joint an adjacent mass of enlarged iliac nodes can be demonstrated

for subcutaneous lymphedema secondary to involvement and obstruction of the subpleural trunks. Although retrosternal infiltration with presternal edema may be seen without evidence of sternal involvement, Fleischner *et al.* (19)



FIG. 10. Hodgkin's Disease. There are areas of bone destruction in the left iliac bone adjacent to the sacro-iliac joint. The diseased areas are slightly reticulated by surviving trabeculae. The lesions do not give the impression of being rapidly invasive. The margins, while not sharp, are not difficult to delineate. There was also a mixed lesion of the first lumbar vertebra.

found that in the majority of their cases presternal swelling was followed *in a matter of months* by invasion of the sternum. When it can be demonstrated that the sternum is affected the presternal swelling may represent actual lymphoma,

in the pelvis by obliteration of the normal soft tissue shadows of the obturator internus and psoas muscles as they cross the pelvic cavity or by displacement of a contrast-filled ureter. The association of the sclerotic bone lesion with an adjacent pelvic mass is then strongly suggestive of lymphoma. Strangely enough, the majority of these lesions occur on the right side. In this case no pelvic mass could be demonstrated on the plain film. Urographic studies were not done.

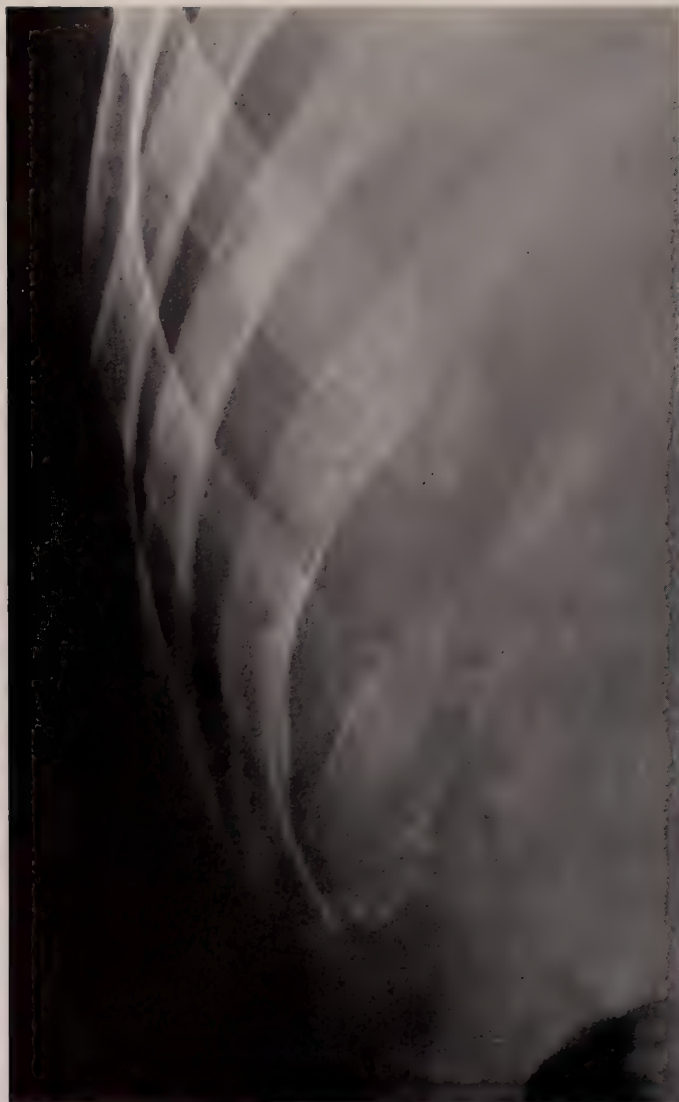


FIG. 11. Hodgkin's Disease. There is a destructive process involving the eleventh right rib with expansion of the bone contour. The cortex is thinned and perforated in some areas. Lytic lesions can be seen in the ribs above. This patient had a large right pleural effusion without evidence of intrathoracic node enlargement.

secondary lymphedema or both. The anterior mediastinal lymph nodes are enlarged in some cases of Hodgkin's disease without involvement of the hilar or other mediastinal nodes. Some cases showing this isolated anterior mediastinal lymphadenopathy have been noted to later develop the plaque-like retrosternal infiltration described above (19).

The Long Bones

In keeping with the usual distribution of red marrow in older adolescents and adults, Hodgkin's lesions in long bones occur predominantly in the proximal ends of the femur and humerus. In some instances, however, the lesions may



FIG. 12. Hodgkin's Disease. The manubrium sterni is involved by a mixed lytic and blastic process. No anterior mediastinal adenopathy was noted but there was a retromanubrial soft tissue plaque and swelling anterior to the bone.

involve a greater portion or all of the shaft or may be localized to the distal metaphysis. The pathologic process may be manifested as pure osteolysis, mixed blastic and lytic changes or osteosclerosis. Various reports stress one type or another but, at least in our experience, lytic lesions have been those most commonly found. Areas of bone destruction may be solitary but are more often

multiple. They may be well margined, even with a border of increased density or they may merge with the adjacent normal bone (Figs. 14, 15). A characteristic pattern, which may be seen *in all forms of malignant lymphoma* involving bone, including leukemia, is that of multiple small lucencies extending for some distance into the shaft. *These are usually elliptical or linear in shape, their long*



FIG. 13. Hodgkin's Disease. There is a mixed lesion of the manubrium. Bony spicules extend anteriorly from the sternum into a presternal soft tissue mass. The spicules are perpendicular to the involved bone and present a "sun-burst" appearance. There is also a thickened retrosternal plaque of soft tissue convexed posteriorly with its base toward the sternum.

axes running parallel to the long axis of the shaft. Frequently this type of marrow involvement is associated with multiple areas of erosion along the inner aspect of the cortex (Fig. 16). The scalloped appearance thus produced is similar to that which may occur in other conditions where masses of proliferating cells are scattered through the marrow. We have found the small elliptical and linear lucencies with long axes parallel to the long axis of the shaft predominantly in malignant lymphomas and in Gaucher's disease. They are far more common in the lymphomas, however, and we have found them to be of considerable



FIG. 14. Hodgkin's Disease. There are several large areas of bone destruction in the head of the left humerus and in the adjacent glenoid. The diseased areas are trabeculated by surviving trabeculae and are well margined. In some areas the lesions have borders of increased density. Multiple small lucencies extend well into the humeral shaft. Most of them are elliptical or linear with their long axes parallel to the long axis of the shaft. Secl-
loping of the inner aspect of the cortex can be seen also. The lesions in the scapula and humeral head give the impression of relatively slow growth.



FIG. 15. Hodgkin's Disease. There is a large area of bone destruction in the upper shaft of the right femur. The lesion is well margined and is crisscrossed by surviving trabeculae. There are numerous smaller areas of destruction above and below the larger lesion.



FIG. 16. Hodgkin's Disease. There are numerous small lucencies throughout the marrow cavity of the right humerus. Most of them are elliptical or linear with their long axes parallel to the long axis of the shaft. In many areas there is scalloping of the inner aspect of the cortex. This pattern, while not pathognomonic, is characteristic of malignant lymphoma and leukemia. The patient was a 33 year old male who had mixed lesions of the second and seventh cervical and eleventh dorsal vertebrae. There was also a mottled destructive lesion of the right iliac bone.

diagnostic value. While a somewhat similar pattern may occur in myelomatosis the lucencies in that condition are usually round and generally larger. More characteristically, of course, they have a "punched-out" appearance. In Gaucher's disease such lesions are often accompanied by irregular expansion of the affected bone and associated osteoblastic reaction is more frequent than in the lymphomas. A periosteal reaction of mild degree may occur adjacent to such lesions in lymphomas. Periosteal reaction in Gaucher's disease, while it may occur, is distinctly uncommon and usually of the most minimal degree. Of more significance, however, is the fact that this type of lesion is characteristic of malignant lymphoma but relatively uncommon in Gaucher's disease.

In the long bones lytic lesions may be crisscrossed by trabeculae producing a reticulated pattern. On rare occasions there may be a honeycomb pattern (Fig. 17). An osteoblastic reaction sometimes develops at the periphery of a lesion or within it. Purely osteosclerotic changes can occasionally be seen in the long bones and these too may be accompanied by a mild layer-type periosteal reaction. Thickening of the cortex adjacent to an area of lytic or mixed destruction or to an area of patchy medullary sclerosis is seen in some cases. The medullary cavity under these circumstances is narrowed. In such an instance there may or may not be a moderate periosteal reaction. Such lesions tend to simulate osteomyelitis. Pathological fractures are uncommon with Hodgkin's lesions of the long bones.

Other Bones

The most frequently affected of the other bones are the skull and clavicle. Skull lesions are primarily osteolytic and present no characteristic or distinctive features. The clavicle may be invaded or eroded by supraclavicular or deep inferior cervical glands. The upper margins of the scapula may be similarly involved. The inner ends of the clavicles are sometimes invaded along with the sternum by anterior mediastinal nodes or retrosternal infiltrations.

LYMPHOSARCOMA

The term lymphosarcoma is sometimes used broadly to include all forms of malignant lymphoma except Hodgkin's disease. More often it is restricted to that form of lymphoid tumor in which the basic cell is the lymphocyte or lymphoblast. When the basic cell is the reticulum cell the lymphoma is referred to as reticulum cell sarcoma (stem-cell lymphoma, clasmatoeytic lymphoma). The clinical manifestations and roentgen bone changes are so similar in lymphosarcoma and reticulum cell sarcoma the two conditions can be discussed together. Giant follicle lymphoma will be considered separately.

After puberty there is a sharp rise in the incidence of Hodgkin's disease, the majority of cases occurring between the ages of 20 and 40 years. In the lymphosarcomas there is a more gradual rise in incidence, the highest incidence occurring in individuals between 45 and 65 years of age. In young children before puberty, however, lymphosarcoma occurs more frequently than Hodgkin's disease and is not rare. Charache (20) analyzing 1800 malignant tumors in

children found that 6.3 per cent were lymphosarcomas. Dargeon (21) found that lymphosarcoma comprised 5 per cent of 583 malignant tumors in children treated at the Memorial Hospital in New York City.

In some cases of lymphosarcoma (including reticulum cell sarcoma and giant



FIG. 17. Hodgkin's Disease. There is a typical "honeycomb" pattern of destruction involving the medullary cavity at the upper end of the left femur. The area of destruction is crisscrossed by remaining coarsened trabeculae. There is slight scalloping of the inner aspect of the cortex.

follicle lymphoma) a transition to leukemia occurs. This transformation occurs more frequently in children than in adults. Rosenberg, Diamond and Craver (22) reviewed 1269 cases of lymphosarcoma and found that 7.6 per cent of the total group showed leukemic changes. Among the children of this group transition occurred in 13 per cent. Of all patients those with small cell lympho-

sarcoma showed the highest incidence of leukemic change (12.6 per cent). Of those with giant follicle lymphoma 8.6 per cent underwent this transformation. The transition occurred least often in patients with reticulum cell sarcoma (2.4 per cent). Transformation to leukemia is not seen in Hodgkin's disease.

Parenthetically, some features of lymphosarcoma in children are worth noting briefly. The more recent reviews of relatively large numbers of children with this condition, reported by Rosenberg *et al.* (23), Bailey and associates (24) and Sherman and Wolfson (25) have brought these features into clearer focus. In all malignant lymphomas males are affected more frequently than females. In lymphosarcoma the proportion is approximately 2 to 1 in adults but rises to 3 to 1 in children. Between the ages of 11 and 15 years the ratio of males to females reaches a maximum of 4.5 to 1. Superior vena cava obstruction occurs about four times more frequently in children than in adults. Primary small bowel foci are more common in children and intussusception is the presenting complaint more commonly in the younger age groups. Primary gastric lymphosarcoma is rare in children.

In regard to the occurrence of bone lesions during the span of the disease, Vieta *et al.* (10) found that in Hodgkin's disease in 37 per cent of the cases with bone involvement the bone lesions were demonstrated before one half the course of the disease had elapsed. In 31 per cent the lesions occurred during the last third of the course. On the other hand, in lymphosarcoma only in 22 per cent of the cases were bone lesions demonstrated during the first half of the disease while in 63 per cent they were first noted during the last third. There was a short average survival period after the appearance of bone lesions in lymphosarcoma. This amounted to 5.8 months as compared to 17.6 months in Hodgkin's disease. Although the appearance of osseous involvement is not considered to have any prognostic significance in Hodgkin's disease, in lymphosarcoma it usually means that the disease is approaching termination. It does not mean, however, that the course of the disease has been more rapid than in patients who have had no bone lesions.

Bone Lesions in Lymphosarcoma

Bone involvement may occur, as in Hodgkin's disease, by direct extension from diseased lymph nodes or by hematogenous spread. In addition, it is considered likely by most observers that in some cases reticulum cell sarcoma may arise *de novo* in bone. An accurate estimate of the incidence of bone lesions is difficult for the reasons mentioned above in the discussion of Hodgkin's disease. The usually quoted figures are those of Vieta *et al.* (10) who found radiographic evidence of bone involvement in 7 per cent of 213 cases of all types of lymphosarcoma. It is agreed, however, that bone is affected more often in reticulum cell sarcoma. Coles and Schulz (26) found demonstrable bone lesions in 12 per cent of 81 cases of lymphosarcoma (lymphocytic and lymphoblastic) and in 21 per cent of 58 cases of reticulum cell sarcoma.

The distribution of osseous lesions is essentially similar to that which occurs in Hodgkin's disease, the vertebrae, pelvis, ribs and femora being the most

frequently involved sites. The predominance of lesions in the axial skeleton, however, is not as great as in Hodgkin's disease, the distribution being more general in lymphosarcoma. Thus there is a higher percentage of involvement of the extremities and a lower percentage of involvement of the axial skeleton in lymphosarcoma than in Hodgkin's disease. As will be noted below, in primary reticulum cell sarcoma of bone the distribution is completely reversed so that there is an actual predominance of lesions in the tubular bones.

The roentgen appearance of the lesions is also essentially similar to that of Hodgkin's disease but there are some differences which should be noted. *In lymphosarcoma (including reticulum cell sarcoma) osseous lesions tend to be more rapidly invasive and destructive and are frequently more locally extensive. In addition they are most often osteolytic, in some instances even producing almost total dissolution of the affected part. In Hodgkin's disease bone destruction appears to be more gradual with frequent reactive osteosis. Mixed and sclerotic lesions, while they may be seen in lymphosarcoma, are decidedly less common than in Hodgkin's disease. Vieta et al. (10), for instance, found that in their cases of Hodgkin's disease with bone involvement 58 per cent of the bone lesions were mixed, 28 per cent were osteolytic and 14 per cent were sclerotic, while in lymphosarcoma 85 per cent were osteolytic, 10 per cent were mixed and only 5 per cent were sclerotic.*

In keeping with the more destructive nature of the lesions, pathological fractures are more commonly seen in lymphosarcoma and compression of the vertebral bodies tends to be greater in degree than in Hodgkin's disease. The invasive nature of the lesions also tends to result in loss of sharp margination. At least, poorly defined margins are more common in these lesions than in those of Hodgkin's disease. This is to be understood, however, as a general rule only, as exceptions will not be difficult to find.

Periosteal reaction occurs in approximately one half of the long bone lesions. It is characteristically mild in degree and usually of a single-layer type. Onion-skin and perpendicular types of reaction are rare but do occur. Occasionally a small triangle of periosteal reaction may be seen at one of the lesional margins resembling the periosteal triangle seen more commonly in osteogenic sarcoma.

Periosseous soft tissue mass formation is frequent. In most cases, however, this is not marked. Calcification within such a mass may be noted occasionally.

The most common appearance of lymphosarcoma and reticulum cell sarcoma in bone is that of *rather uniformly mottled, patchy areas of destruction* (Fig. 18). These may or may not be associated with patchy areas of reactive osteosis. The lesions are usually relatively extensive and there is usually evidence of cortical destruction with or without periosteal reaction or moderate periosseous soft tissue mass formation (Figs. 19-22). Elliptical and linear rarefactions usually forming a relatively uniform pattern with their long axes parallel to the long axis of the shaft are common in the long bones and form a pattern which we consider distinctive of the malignant lymphomas and leukemia. Irregular or rounded areas of lysis, however, may be seen. In some cases the lytic processes may not be readily perceptible or may be difficult to distinguish from a normal

bone pattern. Attention may be drawn to these by an adjacent mild periosteal reaction (Fig. 23).

It is not intended to suggest that differentiation between a Hodgkin's and lymphosarcomatous bone lesion can often be made with confidence. It may be said, however, that in the presence of lymphomatous disease elsewhere, an extensive, invasive, osteolytic process should suggest lymphosarcoma while a more moderately destructive mixed blastic and lytic lesion should suggest Hodgkin's disease (10). Sclerotic lesions in the spine and pelvis favor a diagnosis of Hodgkin's disease. The lesions of lymphosarcoma, when multiple, have a greater tendency to be of similar character. *In those instances where the lesional pattern differs in different bony parts a diagnosis of Hodgkin's disease should be favored.* For instance, a mottled predominantly lytic lesion in the pelvis or in a long bone associated with a mixed or sclerotic lesion in the spine should suggest Hodgkin's disease. This rule will be helpful in most cases but exceptions to it should cause no surprise.

PRIMARY RETICULUM CELL SARCOMA OF BONE

There appears to be increasing acceptance of the concept that reticulum cell sarcoma, in occasional cases, may arise as a primary localized tumor of bone. Parker and Jackson (27) presented the first group of such cases in 1939 when they reviewed 17 cases of what they called primary reticulum cell sarcoma of bone, emphasizing the difference between them and reticulum cell sarcoma of bone secondary to generalized reticulum cell sarcoma. In the same year Ewing (28) recognized the condition as a distinct entity when he included it in his revised classification of bone tumors. Since then several confirmatory series have been published. Among the larger of these have been the reports of Sherman and Snyder (29), Coley, Higinbotham and Groesbeck (30) and Wilson and Pugh (31). It should be added, however, that complete agreement regarding the histogenesis of these tumors is not to be found. The total clinico-pathological picture, nevertheless, is considered to be characteristic and recognition of the condition as a distinct entity is believed by most workers to have a definite practical value. Before the report of Parker and Jackson most cases were diagnosed as Ewing's sarcoma, osteogenic sarcoma or metastatic disease. The fact that primary reticulum cell sarcoma of bone has a distinctly more favorable prognosis than other malignant bone tumors for which it may be mistaken would appear to warrant its recognition as a separate entity even if only for clinical purposes.

The established criteria for the diagnosis of primary reticulum cell sarcoma of bone (30, 32) are considered to be as follows: 1.) The primary focus should originate in a single bone; 2.) Biopsy material should be obtained from the bone lesion; 3.) The histologic pattern should be similar to that of reticulum cell sarcoma arising in other tissues; 4.) There should be a long natural history without generalized symptoms; 5.) Metastatic lesions should be limited to the regional lymph nodes or not make their appearance within six months of the primary and 6.) The neoplasm should be highly radiosensitive. Some authors consider these criteria to be unduly rigid and recently Nolan (33) has made some

interesting comments in this regard. According to his view, the stringent application of the above criteria, although insuring that only primary reticulum cell sarcoma of bone is included, may well exclude cases in which the disease may take a different course. In other words, it tends to select a group of cases in which the course may be more benign than that of reticulum cell sarcoma of bone as a



FIG. 18. Generalized Reticulum Cell Sarcoma. The eighth right rib is the site of rather uniform mottled destruction.

whole. He suggests that if the criteria were realistically relaxed to require only that the histologically characteristic lesion be initially restricted to bone with or without regional lymph node involvement, the resulting alteration in the overall prognosis would justify less optimism than now exists in regard to this condition. There is no doubt that primary reticulum cell sarcoma of bone with a favorable clinical history is deserving of a hopeful prognosis but Nolan suggests that the condition may well have a range of behavior extending from highly malignant and rapidly fatal to relatively benign and curable. As evidence



FIG. 19. Generalized Reticulum Cell Sarcoma. There is mottled destruction of the right iliac bone and acetabulum with multiple pathological fractures. Numerous small areas of lysis are scattered throughout the involved bone. A similar process is seen in the right femur but in this long bone the small lucent areas tend to be elliptical and linear with the long axes parallel to the long axis of the shaft. There is scalloping of the inner aspects of the regional cortices. The entire process involved the right pelvis and most of the right femur. The soft tissues lateral to the pelvis are swollen. The patient was a 56 year old female. At autopsy there was diffuse intrathoracic and abdominal lymphadenopathy. The liver, brain and left kidney were also involved by the pathological process.



FIG. 20. Generalized Reticulum Cell Sarcoma. There are numerous small rounded areas of destruction in the head and neck of the left femur. In the marrow cavity of the shaft the lytic lesions are mostly elliptical and linear. The medial femoral cortex is diffusely involved by the destructive process. There is extensive and advanced destruction of the left pubis and ischium. A soft tissue mass protruding into the pelvis can be seen above and adjacent to this extensive lymphomatous process. The similarity of the pattern of bone involvement to that shown in Fig. 19 is striking.

favoring this attitude he has directed attention to the fact that in the case of several other malignant neoplasms the patient with a localized lesion and a long antecedent history has a more favorable prognosis than otherwise.



FIG. 21. Generalized Lymphosarcoma. There is a localized area of mottled bone destruction in the upper third of the left femur. Some scalloping of the regional cortices may be noted and some of the lytic lesions tend to be linear or elliptical. The patient was a 60 year old female. Osteolytic changes were also present in both humeri and three dorsal vertebrae were collapsed by diffuse destructive changes.

Taken on the basis of the presently accepted criteria, primary reticulum cell sarcomas of bone tend to pursue a relatively slow course. In some cases the pathologic process may remain localized to the site of origin for long periods



FIG. 22. Generalized Lymphosarcoma. There is a large destructive lesion involving the right iliac bone. The process has destroyed a portion of the cortex and has produced an adjacent soft tissue mass.

of time. In others, the process may spread locally to involve the regional lymph nodes. In either case the lesions are often curable by radiation. If in an accessible site they may be cured by radiation or amputation. Sometimes even after successful therapy of the original lesion a similar involvement may develop in other bones several years later. In still other cases despite apparently successful treatment of the primary lesion the disease becomes generalized, the terminal picture being similar to that of generalized reticulum cell sarcoma. If one is mindful of the variations in course which may occur in this disease, however, it becomes apparent that in any given case caution should be exercised in regard to the ultimate prognosis.

The literature on this condition reveals numerous conflicting opinions regard-



FIG. 23. Generalized Lymphosarcoma. The lower end of the femur is the site of numerous scattered small irregular lucencies which are not outstanding. Although the adjacent cortex appears intact, there is a minimal periosteal reaction along the medial aspect of the bone.

ing the age distribution but the total picture to date suggests that after the age of 9 or 10 the occurrence of primary reticulum cell sarcoma of bone is more or less evenly distributed throughout the life span. There may be a slight predominance of cases between the ages of 20 and 40 years. The age incidence differs from that of Ewing's tumor which, in the vast majority of cases, occurs in childhood and adolescence or before the age of 30 years. It differs also from gener-

alized reticulum cell sarcoma which occurs predominantly in patients over 40 years of age. Males are more frequently affected than females, the proportion being approximately 2 to 1.

Almost any portion of the skeleton may be affected. Lesions in the mandible, ribs, pelvis, vertebrae and scapulae are not uncommon and at least three cases involving the skull have been described (34), but *there is a definite predilection for the long tubular bones, especially those of the lower extremities*. In 23 of 33 cases reported by Wilson and Pugh (31) the lesion arose in the tubular bones. Fifteen of these were in the lower extremities and eight were in the upper extremities. In 10 of the 17 cases reported by Sherman and Snyder (29) the sites of origin were in the lower extremities while 2 were in the upper extremities. This predilection for the extremities is apparent in practically all reports of sizable series. If the cases reported by Parker and Jackson (27), Sherman and Snyder (29) and Wilson and Pugh (31) are combined it will be found that the diseased site involved an extremity in two-thirds of the cases (46 of 67 cases). It is important to note also that *when a lower extremity is affected the lesion is usually in the region of the knee*. In fact, about forty per cent of all primary reticulum cell sarcomas of bone occur at the lower portion of the femur or upper portion of the tibia. When the upper extremity is affected the lesion most often arises at the proximal end of the humerus.

Symptomatology is usually limited to bone pain at the involved site and in most cases there is some regional swelling which is seldom of more than moderate degree. Wilson and Pugh (31) found soft tissue swelling at the site of the lesion in 85 per cent of 33 cases. A characteristic clinical feature of this disease is the general well being of the patient. There are seldom any constitutional symptoms. Loss of weight, low grade fever and easy fatigability such as are commonly seen in patients with other types of malignant bone tumor are absent in most cases.

In regard to the roentgen appearance it should be made clear at the outset that the pattern of bone change in this condition cannot be differentiated from the changes which occur in a single bone secondary to generalized reticulum cell sarcoma. The pathologic process arises in the medullary cavity. In the majority of cases the dominant change is one of mottled destruction (Fig. 24). Frequently the small areas of lysis are elliptical or linear with their long axes parallel to the long axis of the shaft. The area of destruction is usually rather extensive. Some patchy areas of destruction may be combined with similar sized areas of bone production. Advanced destruction occasionally results in complete dissolution of large segments of bone (Fig. 25). Although in most cases bone destruction is predominant, in some instances reactive proliferation of bone may be of equal prominence or, less commonly, dominates the roentgen pattern. There is seldom any sharp margination of the lesions, the borders of which are poorly defined. Some degree of cortical destruction is usually present. In approximately half the cases there is a mild periosteal reaction, characteristically of the "layer" type. In the early stages of some cases periosteal reaction may *precede* roentgen evidence of medullary or cortical bone destruction (35). Occasionally there is



FIG. 24. Primary Reticulum Cell Sarcoma of Bone. There are mixed destructive and productive changes with pathological fracture at the upper end of the right humerus. The patient was a 44 year old female whose history was that of pain in the right shoulder of 1½ years duration. There were no constitutional symptoms and no evidence of lymphomatous disease elsewhere. The lesion was treated by x-ray therapy. There was no evidence of extension of the disease when the patient was last seen one year later.

moderate thickening of the regional cortex. Periosseous soft tissue involvement is not uncommon but it does not reach marked proportions. Calcification within such soft tissue masses may occur but usually there is none. Pathological fractures are not uncommon, particularly in the long bones. When the lesion is



FIG. 25. Primary Reticulum Cell Sarcoma of Bone. There is extensive involvement of the lower end of the femur by a destructive process which has resulted in complete dissolution of the anterior aspect of the bone and has thinned the posterior cortex which is also perforated in some areas. A large soft tissue mass extends anteriorly compressing the adjacent tendons and displacing the patella downward. There has apparently been a pathological fracture through the supracondylar area. The patient was a 62 year old female who maintained that she first noticed pain and limitation of motion at the right knee four months before admission to the hospital. On examination there was a large, firm, slightly tender mass at the lower end of the right femur. Several firm nontender nodes were palpable in the right inguinal region. There was also evidence of hypertensive heart disease with mild congestive failure. Biopsy of the diseased bone and the inguinal lymph nodes revealed reticulum cell sarcoma. At the time there was no evidence of lymphomatous disease elsewhere. Four months later generalized lymphadenopathy developed and the patient ran a downhill course, complicated by infection following biopsy, and by heart failure. She died about 4½ months after admission showing evidence of generalized reticulum cell sarcoma.

situated in the region of the knee there may be a synovitis. This may be the most prominent feature in the early stages of some cases and may be misleading if evidence of bone destruction is equivocal or absent. Fripp and Sissons (35) have

reported a case in which joint effusion and minimal periosteal reaction were present early without evidence of medullary or cortical bone destruction.

GIANT FOLLICLE LYMPHOMA

(Brill-Symmer's Disease)

Although sporadic descriptions of this condition appeared between 1901 and 1921 (36-39) attention was not called to it in this country until 1925 when Brill, Baehr and Rosenthal (40) reported two cases of what they called "generalized giant follicle hyperplasia of lymph nodes and spleen." The process was at first considered to be benign (40, 41) but later Baehr and Rosenthal (42) and Baehr, Klemperer and Rosenthal (43) concluded that the disease is a form of lymphosarcoma "distinguished by its characteristic pathology, its unique pathogenetic evolution and its unusual duration." The latter authors proposed the term "follicular lymphoblastoma" to designate the condition. Symmers (44) reviewed 25 cases in 1938 showing that some of them terminated in polymorphous-cell sarcoma, lymphatic leukemia or Hodgkin's disease. Baggenstoss and Heck (45) later analyzed 59 cases from the literature and 13 of their own and agreed with Baehr, Klemperer and Rosenthal that the disease is a form of lymphosarcoma which presents the picture of follicular hyperplasia in its early stage but later is characterized by a conglomeration of the follicles and diffuse infiltration of the lymph nodes by polymorphous lymphoblasts.

With study of the evolution of more cases the clinico-pathological picture has become somewhat less clouded but it is still not completely clear. The disease is characterized by an increase in the number and size of the lymph follicles and a moderately benign course. The follicles are scattered throughout the substance of the node instead of being limited to the periphery and are surrounded by a zone of small lymphocytes. There is a tendency for the follicles to fuse. The interfollicular tissue is densely packed with cells, the trabeculae are obscured and the lymph sinuses are narrowed or obliterated. The capsule may be invaded. In most cases there is eventual transformation into lymphosarcoma, reticulum cell sarcoma, lymphocytic leukemia, or, rarely, Hodgkin's disease. In such instances there is fusion of the follicles and the nodal architecture is obscured, the histologic appearance becoming that of the lymphoma into which it has been transformed. In some instances, however, the follicular pattern may be retained throughout the course of the disease.

Splenomegaly occurs in about sixty per cent of the cases and on occasion the spleen may be enlarged to quite a marked degree. There is usually no anemia or marked debility until the *late* stages of the disease. A tendency to lymphatic infiltration of the lacrimal gland has been noted, sometimes giving rise to a unilateral exophthalmus. The serous membranes are not infrequently involved with resultant pleural or peritoneal effusions which in some cases may be chylous. The pathological tissue, especially during the earlier more benign period, is extremely radiosensitive. Giant follicle lymphoma is, in fact, the most radiosensitive of all the malignant lymphomas. There is some difference of opinion as to whether, in its early stages, the condition is curable by radiation therapy,

but certainly some very long-term remissions may be accomplished by this type of treatment.

Bone Changes in Giant Follicle Lymphoma

Bone changes similar to those which may occur in other forms of malignant lymphoma have been described in some cases. Kenney (46) reported a case with extensive osseous involvement. There was a diffuse destructive process involving most of the skeleton including the skull. The pathology indicated that transformation to lymphosarcoma had already occurred. Meyer (47) has reported six cases of "follicular lymphoblastoma" in two of which bone involvement was demonstrated radiographically. In one case there were areas of increased density in the ischial rami and a suggestion of mottling at the upper ends of the femora. The patient was a 46 year old female who had cervical, axillary and inguinal lymphadenopathy without enlargement of the spleen or liver for a period of three years before coming under observation. The microscopic pathology was described as showing giant follicles separated by a lymphoid stroma within which there were numerous eosinophils but no Reed-Sternberg cells. The condition was diagnosed as giant follicle lymphoblastoma. Death occurred two months after the first examination. In the other case there was an area of destruction in the lower femur which showed characteristic patchy areas of lucency with cortical erosion and perforation. The patient had been observed for four years, biopsy showing a transformation of the lesion to lymphosarcoma but with some retention of the follicular character of the nodal architecture. The bone lesion was discovered about three years after the first observation and about eight months before death. Rappaport *et al.* (48) found bone involvement in 19 of 134 cases (14 per cent). The distribution of the osseous lesions was similar to that for lymphosarcoma in general. The lesions were osteolytic in eighteen cases and osteoblastic in only one. *In all cases the disease had progressed to the point where there was clinical evidence of widely disseminated lymphoma by the time bone changes were demonstrated.*

It appears, therefore, that bone changes occur in the late stages of follicular lymphoma, have a distribution similar to that for lymphosarcoma in general, and are predominantly osteolytic in type. They may be demonstrated in cases where the histologic picture has become that of one of the diffuse forms of lymphosarcoma or in cases in which a follicular pattern has been retained until death.

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UTERINE CERVIX "CARCINOMA IN SITU"

VALIDITY OF BIOLOGIC CONCEPT VS. CLINICAL ENTITY

HERBERT E. NIEBURGS, M.D.

New York, N. Y.

The existence of a carcinomatous epithelial alteration without stromal invasion was first described in 1908 as "Oberflächencarcinom" by Schauenstein (1) and in 1909 by Pronai (2). Further observations were reported by Rubin in 1910 using the term "incipient carcinoma" (3) and Schottlaender and Kermanner in 1912 (4). Broders (5) in 1932 was the first to introduce the term "carcinoma in situ." Hinselman (6) in his classification used "increasingly atypical epithelium" (*gesteigertes atypisches epithelium*) and "atypical carcinoid epithelium." The terms "preinvasive carcinoma" and "surface carcinoma" were suggested by Schiller (7) in 1937 and "intraepithelial carcinoma" by Galvin and TeLinde (8) in 1948. The accepted designation of "Stage 0" for this lesion was initially recommended by J. H. Mueller in 1941 (9). Since then, the literature has been enriched by publications on numerous aspects of "carcinoma in situ."

The term "carcinoma in situ," which is used for the description of a carcinomatous epithelial alteration above an intact basement membrane, carries also the prognostic connotation of malignant transformation to invasive carcinoma. When the diagnosis is made on the basis of biopsies from some parts of the cervix, it may not always convey the true condition of the lesion. In such cases, stromal infiltration may exist in the remaining cervical tissue of the patient at the time when the diagnosis of "carcinoma in situ" is rendered.

The detection by cytologic methods of an increasing number of "non-invasive" lesions has led to many publications on the rate of progression to invasive carcinoma, the period of latency, spontaneous regression and other aspects of "carcinoma in situ." Evidence has been insufficient as to which stage of epithelial alteration may be regarded with certainty as a precursor to invasive carcinoma, and opinions differ widely as to which of the epithelial alterations constitutes "carcinoma in situ." Therefore, the rate of progression to invasive carcinoma is also related to the diagnostic criteria which are used for the histopathologic interpretation of the "in situ" lesion.

THE BIOLOGIC CONCEPT OF "CARCINOMA IN SITU"

There is little doubt that "carcinoma in situ" and earlier epithelial changes represent different stages of malignant transformation. The frequently observed coexistence of such epithelial alterations with areas of invasive carcinoma lends support to this contention (Table I). Often, the same specimen may contain all grades of transition from minor epithelial changes to those with carcinoma, possibly reflecting the stages of development to invasive carcinoma.

Retrospective studies of available biopsies obtained one to twenty years prior

From the Department of Pathology, The Mount Sinai Hospital, New York, N.Y.

to the diagnosis of invasive carcinoma revealed the presence of tissue changes which had been designated as "carcinoma in situ," "increasingly atypical epithelium," "irregular epithelium," "simple atypical epithelium" and "basal cell hyperactivity" (Table II). These findings seem to indicate that invasive carcinoma had developed through various stages of transition, but there is no evidence as to which of the tissue alterations sets the irreversible stage for malignant tumor transformation.

The significance of tissue changes as precursors to carcinoma was studied by

TABLE I
Comparative Data on the Coexistence of Different Cervical Lesions

Authors	Type of Epithelial Alteration				Percentage
	Dysplasia	Anaplasia	Ca in situ	Invasive Ca	
Fluhmann (10)	+		+		32.5
Reagan (11)	+		+		82.0
McKay (12)		+	+		88.0
"		+		+	12.0

TABLE II
Comparison of Retrospective Findings in Biopsies 1-20 Years Previously

Final Diagnoses	No. of Patients	Initial Diagnoses						Years
		Carcinoma in situ	Increasingly Atypical Epithelium	Irregular Epithelium	Simple Atypical Epithelium	Basal Cell Hyperactivity	Normal	
Invasive Carcinoma	24 (13)	70.8%				12.5%	16.7%	1-20
	10 (14)	100.0%						1-17
	2 (15)		100.0%					10
Ca in situ (Surface Ca)	15 (13)	26.6%				66.6%	6.6%	1-10
	3 (14)	100.0%						2, 4, 6
	13 (15)			38.0%				
Benign	47 (14)		4.3%		95.7%			4

the observation of various cervical lesions in untreated patients for periods of many years. Although in some patients with dysplasia and "carcinoma in situ" the lesions developed subsequently to invasive carcinoma, in other cases the lesions remained unchanged or regressed (Table III). This inconsistent behavior of lesions may be in keeping with the discrepancy between the rate of diagnosed "carcinoma in situ" lesions (400-900 per 100,000) and the incidence of invasive cervix carcinoma (26-44 per 100,000).

Period of Transition from "Carcinoma in situ" to Invasive Carcinoma

It was earlier suggested that the transition of "carcinoma in situ" to invasive carcinoma occurred in an average period of ten years (30, 31). This conclusion

was based on the difference of ten years between the average age of patients with "carcinoma in situ" and that of patients with invasive carcinoma. About eighty per cent of women with "carcinoma in situ" are asymptomatic (22, 33). Therefore, this lesion is usually diagnosed by routine examinations with a certain amount of self-selection of women. The prevalence rate for this lesion varies only slightly in the different younger age groups (34), and any predominance in the number of women screened at one age group leads to the detection of a greater number of "carcinoma in situ" lesions in that particular group. The average age of women with cervical lesions, therefore, deviates towards that age group

TABLE III
Data from Observation of Untreated Lesions

Authors	Initial Diagnoses (No. of Patients)							Subsequent Findings (%)				Years Observation
	Basal Cell Hyperplasia	Irregular Epithelium	Epithelial Hyperactivity	Atypical Hyperplasia	Anaplasia	Borderline Lesions	Carcinoma In Situ	Regression	Persistence	Progression Carcinoma In Situ	Invasive Carcinoma	
Wespi (15)		7						28.5	57.0	14.3		
Boddington (16)	10								70.0		30.0	1-3
Petersen (17)			127					23.6	39.0		26.8	10
McKay (12)					65			40.0	52.3	6.1	1.5	
Reagan (11)				65				53.8	30.7	13.8	1.5	
Koss (18)						20		50.0	25.0	25.0	—	7 mos.-7
							44	29.5	54.5		15.9	1-7
Kottmeier (19)							59				13.6	
							31	38.7			48.3	1-17
Funck-Brentano (20)							124				33.3	9
Masterson (21)							25				16.0	1
											4.0	Later
Sherman (22)							13				25.0	1-20
Lee (23)							53			—		3
Graham (24)							15			—		4-6

in which a larger number of women were examined. When number per age corrected data were computed, the difference between the average age of women with "carcinoma in situ" and those with invasive carcinoma was about three years (35, 36).

CLINICAL ENTITY OF "CARCINOMA IN SITU": DETECTION AND DIAGNOSIS

The histopathologic diagnosis of cervical "carcinoma in situ" implies the absence of stromal invasion. The distinction, however, between carcinoma confined to the epithelial surface and invasive carcinoma cannot be ascertained unless serial sections of the entire uterus are examined.

The prognostic connotation of this diagnosis is only partially in keeping with the results of previous observations. Of several series of women with non-

invasive cervical lesions, the highest rate reported for the transformation to invasive carcinoma is 48.3 per cent after one to seventeen years of observation (19).

The lack of progression to invasive carcinoma in many cases led to the interpretation that not all "carcinoma in situ" lesions had the same malignant potential. In view of the fact that many lesions which are designated as "carcinoma in situ" may have a benign course, a careful reconsideration of the terminology and the diagnostic approach is needed.

Although most authors are in agreement that the diagnosis of "carcinoma in situ" is based on epithelial alterations which resemble invasive carcinoma except for an intact basement membrane, there is a considerable difference of opinion as to criteria regarding cell maturation, differentiation, polarity and epithelial stratification (Table IV). Diagnoses of "carcinoma in situ" made with even minor deviations from the characteristics of the truly preinvasive alteration may be the cause for the differences in the subsequent behavior of the lesion.

The lack of a standard nomenclature and the use of terms such as unquiet epithelium, epithelial instability, atypical hyperplasia, dysplasia, carcinoma in situ, surface carcinoma, preinvasive carcinoma, intraepithelial carcinoma and others may be a source of confusion to the clinician. A cervical lesion with a pathologic report in any of these terms may be either carcinoma or potentially malignant. In the latter case, the lesion may remain unchanged or progress to carcinoma during varying periods of time.

Value and Limitations of Cytologic Diagnoses

The accuracy of cytologic diagnoses is determined by the choice of the technic for cell collection and the knowledge of cell pathology.

The preferred technic is the use of a thin cotton applicator which is introduced into the cervical canal about one-quarter of an inch, twirled around a few times and then transferred with the adherent mucous to a glass slide. The best transfer of the mucous material is obtained by turning the cotton applicator in a direction opposite to that in which it is moved across the slide. This procedure is important because the mucous plug serves as a natural reservoir for any atypical cells which may be present.

The removal of the mucous plug prior to the preparation of smears may lead to false negative findings (39). False negative diagnoses may also occur with the use of lubricating jelly prior to the collection of the specimen and when smears are taken from areas other than the endocervix. The use of any type of spatula may cause unnecessary bleeding, prolong the time of microscopic examination and may in some cases lead to false positive interpretations.

The slides with cervical material may be permitted to dry in air. In the laboratory, the cells are reconstructed by a process of rehydration and then fixed in alcohol before staining. With this procedure, the quality of cellular material is equal to that of immediately alcohol-fixed slides. This method, however, is not recommended for the fixation of cellular material from the endometrium or other sites. To permit air drying of specimens other than cervical and vaginal

smears, a specially prepared surface coating and fixing solution is available (37).

Cytologic Classification and Pathologic Significance

The knowledge for the interpretation of single cell changes in smears is acquired from the pathologic diagnosis of the corresponding tissue of cell origin. Any difficulties and controversial aspects in the histologic interpretation of potentially malignant lesions are, therefore, also reflected in the cytologic evaluation.

TABLE IV
Comparison of Diagnostic Criteria

Morphologic Criteria	Interpretation		
	Benign Lesion	Atypical Lesion	Noninvasive Ca
Cell Maturation	Decreased (10, 25, 27)	Decreased (10, 11) Present at surface (18)	Normal at surface (18) Absent or questionable (25) Absent (26, 27)
Differentiation	Normal (11, 27-29) Decreased (27)	Decreased (25, 27) Present at surface (11)	Normal (10) Absent or questionable (25) Absent (10, 27)
Stratification	Normal (10, 25) Decreased (27)	Normal (10, 15) Fairly good (8) Decreased (27) Absent (25)	Decreased (10) Absent (15, 27)
Parakeratosis or Hyperkeratosis	Present (11, 15, 18, 26, 27)	Present or absent (28, 29)	Absent (27) Present (18)
Cell Polarity	Normal (11, 27-29) Abnormal basal cells (10) Abnormal, reg. or irreg. (27)	Abnormal (11, 28, 29) Abnormal basal cells (10) Abnormal reg. (above basal cells) (27) Abnormal irreg. basal cells (27)	Abnormal (26) Abnormal irreg. (27)

The classification of I to V was first introduced by Papanicolaou to which a deferred classification subsequently was added. The numerical designation for the degree of cellular atypia was selected mainly on the basis of subjective impression. Thus, the comparative evaluation of identical classifications from different institutions reflects more the diagnostic approach of the cytopathologist than the difference in cell morphology or the merits of the technic. The statistical evaluation of the accuracy of cytologic interpretations of cellular changes suggestive of malignant cervical lesions also depends on the diagnostic histopathologic approach to noninvasive carcinoma.

In cases of adequate cervical material in smears, the absence of abnormal

cells is a reliable indication of a normal cervix. The interpretation of class V, which is usually made on the basis of unequivocal malignant tumor cells, is associated with a high degree of accuracy. Any other evaluation, such as that of class III or III+ or IV, reflects some doubt as to the pathologic significance of the cellular changes. The clinical value of these diagnoses is questionable since some cervical lesions with cellular changes, in keeping with class III and IV, failed to develop invasive carcinoma during observation periods up to 11 years (38).

Histocytologic Classification of Cervical Lesions

Several attempts were made to improve the understanding of cellular changes by cytometric evaluation (28, 29). In cases of cervical carcinoma, not all cells in the smear derive from the tumor area. Therefore, the pathologic significance of cellular changes cannot be determined solely from the histopathologic findings without the identification of the histologic area of cell origin. The acquisition of knowledge, however, for the interpretation of histologic changes which precede invasive carcinoma is dependent upon evidence from previous observation of such untreated lesions. The pathologic significance of cellular changes may then be determined from comparative studies of cells in initial smears and tissues from the same lesions (27).

The examination with an oil immersion objective of cells in smears and tissues reveal essentially the same nuclear morphologic characteristics in both specimens. A cytologic classification which is developed on this basis may be applied to the evaluation of cells in smears and tissues and greatly augments the diagnostic accuracy for both. Furthermore, the numerical classification can be replaced by a descriptive report of the pathologic significance of cellular changes.

On the basis of histologic and cytologic changes, tissues may be classified according to benign dysplasia, atypical dysplasia (potentially malignant) and carcinoma. The cytologic changes in smears and tissues are accordingly distinguished by benign, atypical and malignant cellular changes. Evidence of invasive carcinoma is not always found in cells of smear preparations.

In keeping with the definition of "carcinoma," its use in connection with "in situ" lesions should be restricted to tissue changes with all characteristics of carcinoma, except for the presence of an intact basement membrane (Figs. 8 and 9). While invasive carcinoma is mainly interpreted from stromal infiltration by cells, the diagnosis of carcinoma above an intact basement membrane must include the extensive examination of cellular changes in the tissue.

The diagnosis of carcinoma without stromal invasion is, therefore, dependent upon the finding of malignant tumor cells in atypical epithelial alterations. Although the morphology of cells in tumor areas varies, some characteristic nuclear changes in cells are consistently associated solely with carcinoma. This malignant alteration consists of marked nuclear enlargement, heteropyknosis and numerous chromocenters of varying size. The chromatin bands which are attached to the chromocenters vary in length, thickness, pyknosis and spaces between bands (Figs. 8-10). In addition to cells with the characteristic malig-

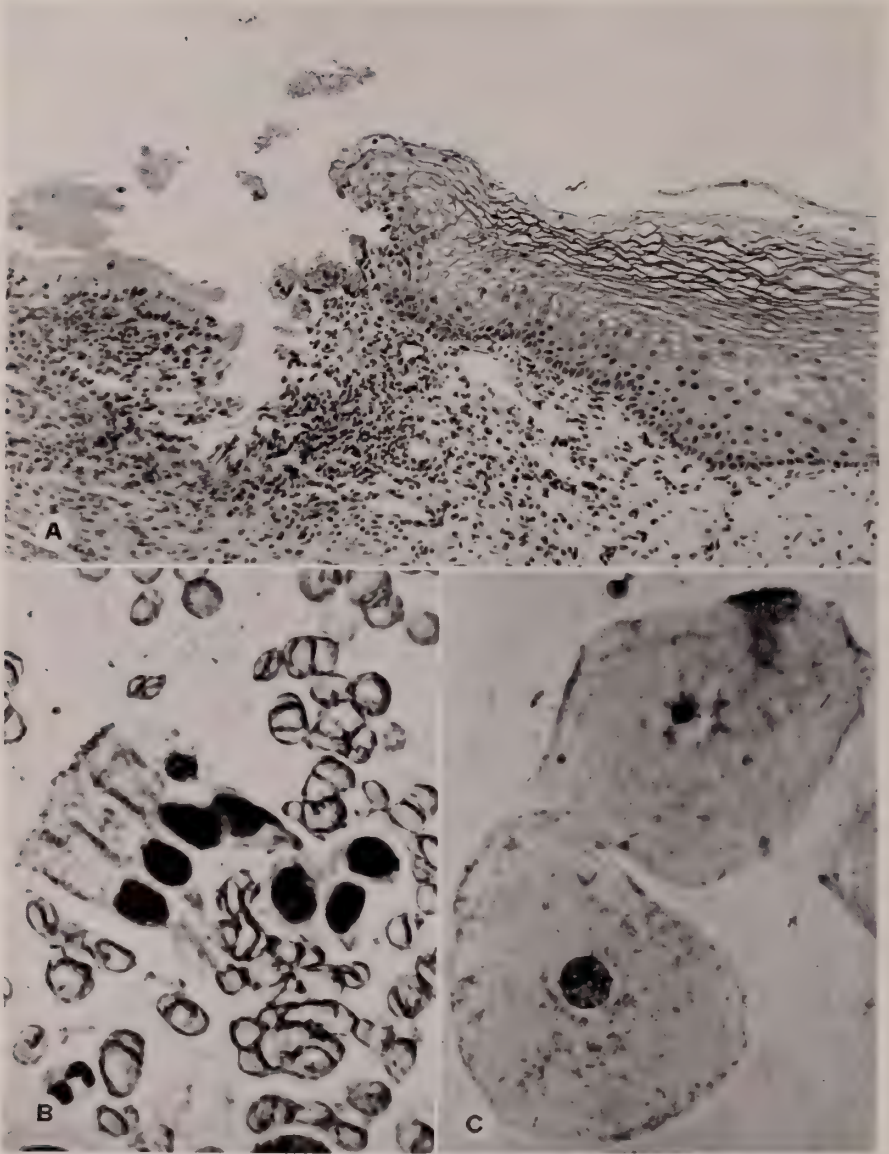


FIG. 1a. Normal squamo-columnar junction of uterine cervix.

FIG. 1b. Cervical smear-columnar cells from the cervical canal.

FIG. 1c. Cervical smear of the portio vaginalis with cells from the surface of the squamous epithelium.

nant alteration, cells with less atypical nuclear changes are frequently also found in the tumor area. The presence of these cells without malignant tumor cells may be noted in areas adjacent to carcinoma or in biopsies preceding the diagnosis of carcinoma.

The malignant tumor cell changes in the tissue are associated with a marked cell maturation defect and absence of cell differentiation with complete loss of

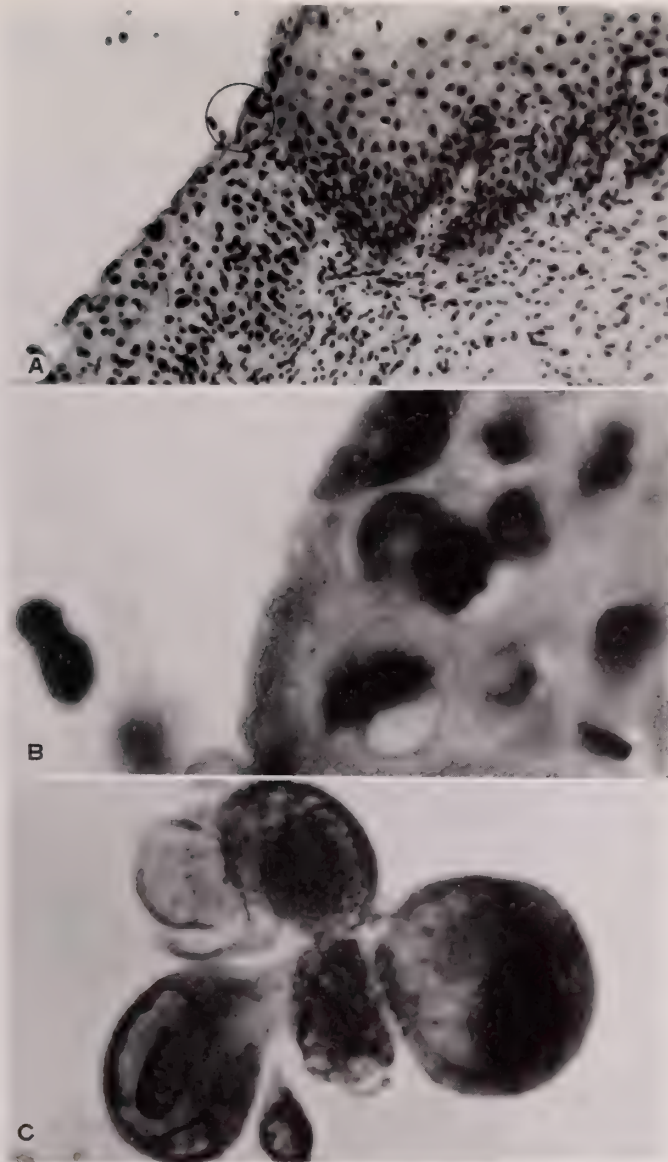


FIG. 2a. Squamo-columnar junction with benign dysplasia in the cervical canal associated with cervicitis ($\times 125$).

FIG. 2b. Surface cells from same case at squamo-columnar junction in the tissue of Fig. 2a ($\times 1000$).

FIG. 2c. Cervical smear with abnormal cells of benign significance associated with *Trichomonas* infection ($\times 1000$).

both stratification and uniform cell polarity. These alterations extend throughout the entire thickness of the epithelium including the basal layer of cells. Such lesions are invariably followed by invasive carcinoma and require the same consideration as Stage I carcinoma.

In cases in which the loss of cell differentiation and of uniform polarity is in-

complete, the histologic interpretation is more dependent upon the cellular changes than in cases of unequivocal carcinoma without stromal infiltration. The benign or potentially malignant significance of the lesion is thus determined by the characteristic differences in the morphology of cell nuclei.

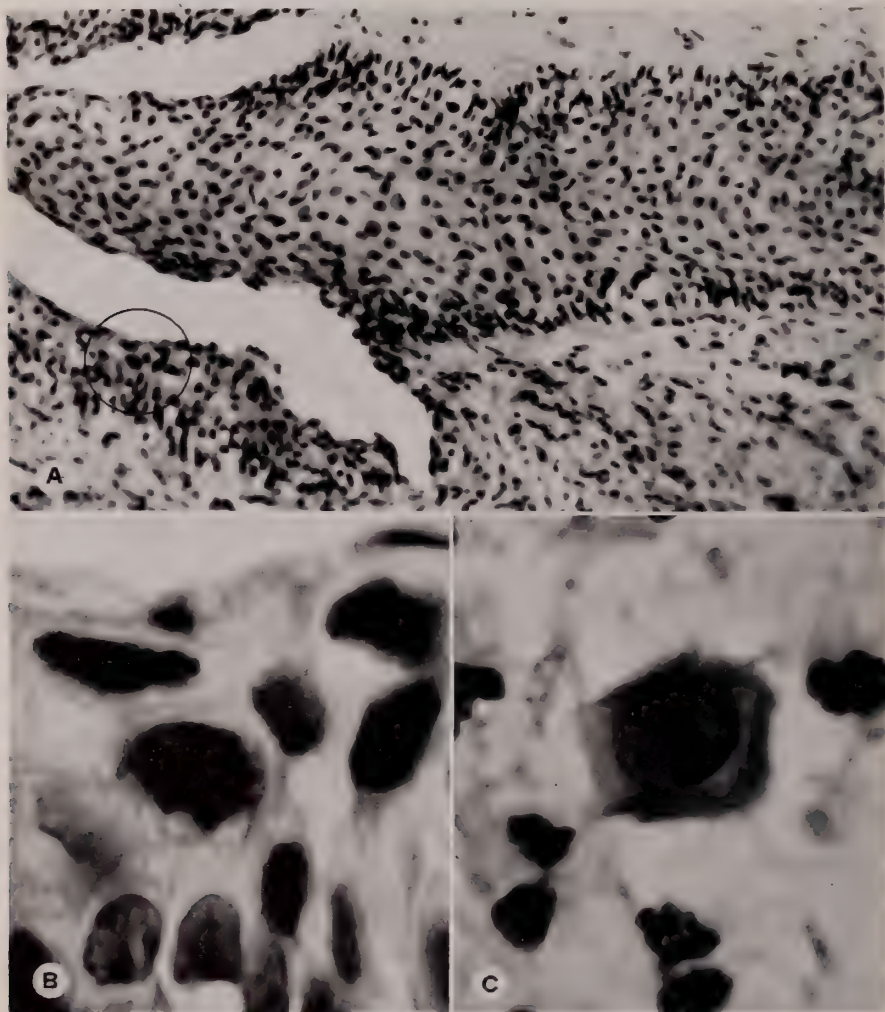


FIG. 3a. Metaplasia with benign cellular changes in cervical gland ($\times 125$).

FIG. 3b. Higher magnification ($\times 1000$) of abnormal cells in Fig. 3a.

FIG 3c. Cervical smear with an abnormal cell of benign significance from the same lesion ($\times 1000$).

The nuclear changes of the potentially malignant lesion of atypical dysplasia consist of increased nuclear size, moderate heteropyknosis, numerous nucleolar bodies with increased associated chromatin and slight variation in length, thickness, staining reaction and distribution of chromatin bands. Cells with these alterations may not be found in the entire thickness of the epithelium but are always present in some areas of the basal layer cells (Fig. 7).

Benign cervical lesions include a large variety of histologic alterations without the presence of cellular changes which are characteristic for potentially malignant lesions or carcinoma. In such lesions, smears and tissues may contain bizarre, often multinucleated cells, marked nuclear enlargement and marked

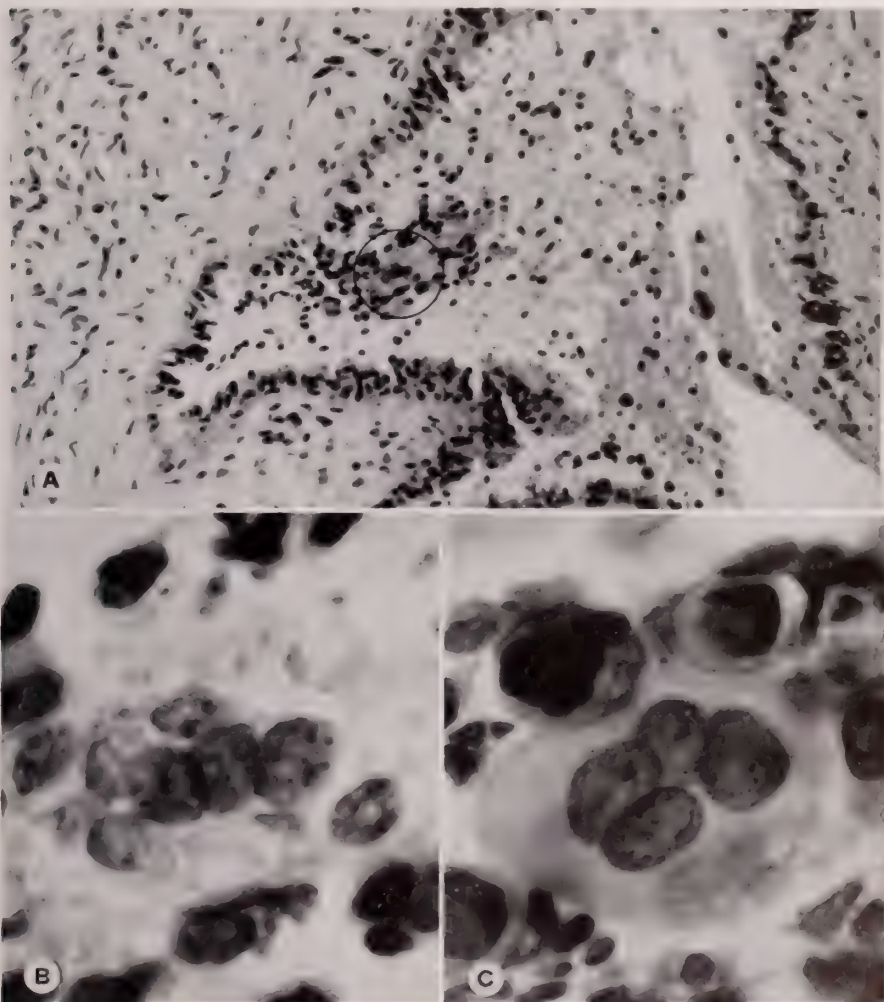


FIG. 4a. Cervical gland with multinucleated cells ($\times 125$). Focal hyperplasia of the squamous epithelium and cervicitis was present in other areas. No evidence of carcinoma was found.

FIG. 4b. Higher magnification of cell in Fig. 4a ($\times 1000$).

FIG. 4c. Cervical smear with benign multinucleated cells of the same patient ($\times 1000$).

pyknosis of the nuclear chromatin often in irregular clumps but without a distinct nuclear structure (Fig. 2-6).

CONCLUSION

The classification based on cellular changes in smears and tissues permits the distinction of benign dysplasia from atypical dysplasia. The diagnosis of car-

cinoma is based upon the finding of characteristic malignant tumor cells in atypical tissue alterations.

In smears, the finding of atypical cellular changes creates some diagnostic problems. These cells, if representative of the entire lesion, reflect the potentially malignant tissue change of atypical dysplasia and the absence of invasive or noninvasive carcinoma. Since, however, the adequate sampling of cytologic material is always questionable, repeat smears or cervical biopsy is recommended in such cases.

A cytologic diagnosis of carcinoma according to this classification is usually associated with either invasive carcinoma or an unequivocal carcinomatous epithelial alteration, although evidence of stromal invasion may not be present in the tissue available for examination. In cases without evidence of stromal invasion, the cytologic changes in the tissue are of a malignant character.

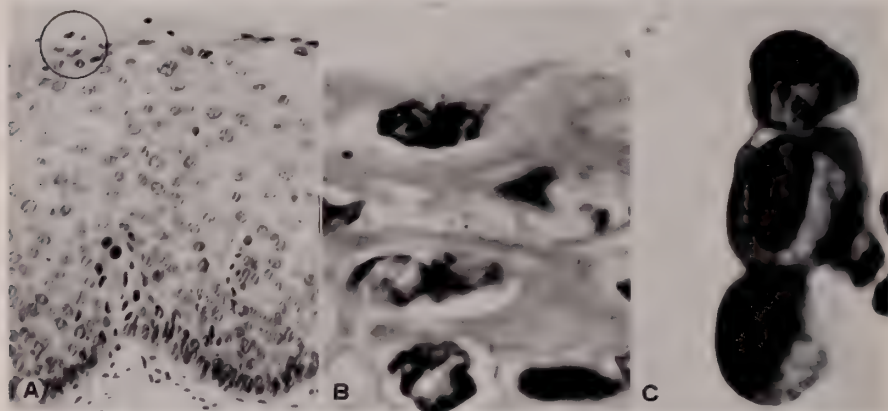


FIG. 5a. Tissue with basal cell proliferation associated with *Trichomonas* infection ($\times 125$).

FIG. 5b. Higher magnification of cells in Fig. 5a ($\times 1000$).

FIG. 5c. Cervical smear with benign cellular changes from the same lesion ($\times 1000$).

Some doubt is cast on the validity of "carcinoma in situ" as a clinical entity. Although probably all invasive carcinomas develop through a stage of "carcinoma in situ," diagnostic limitations preclude the interpretation of this stage of malignant transformation unless the entire uterus is available for examination.

Based upon the premise that "carcinoma in situ" except for stromal invasion has all the characteristics of carcinoma, the diagnosis of "carcinoma in situ" is neither possible from cytologic smears nor from biopsy sections. Smears with the characteristic cellular changes of carcinoma lack any indication as to whether the tissue contains an intact basement membrane or stromal infiltration. Atypical cells without malignant tumor changes have either benign nuclear characteristics or those associated with atypical dysplasia. In tissue sections, the diagnosis of "carcinoma in situ" does not apply to that part of tissue which has remained in the patient's cervix and may be, therefore, associated with invasive carcinoma.

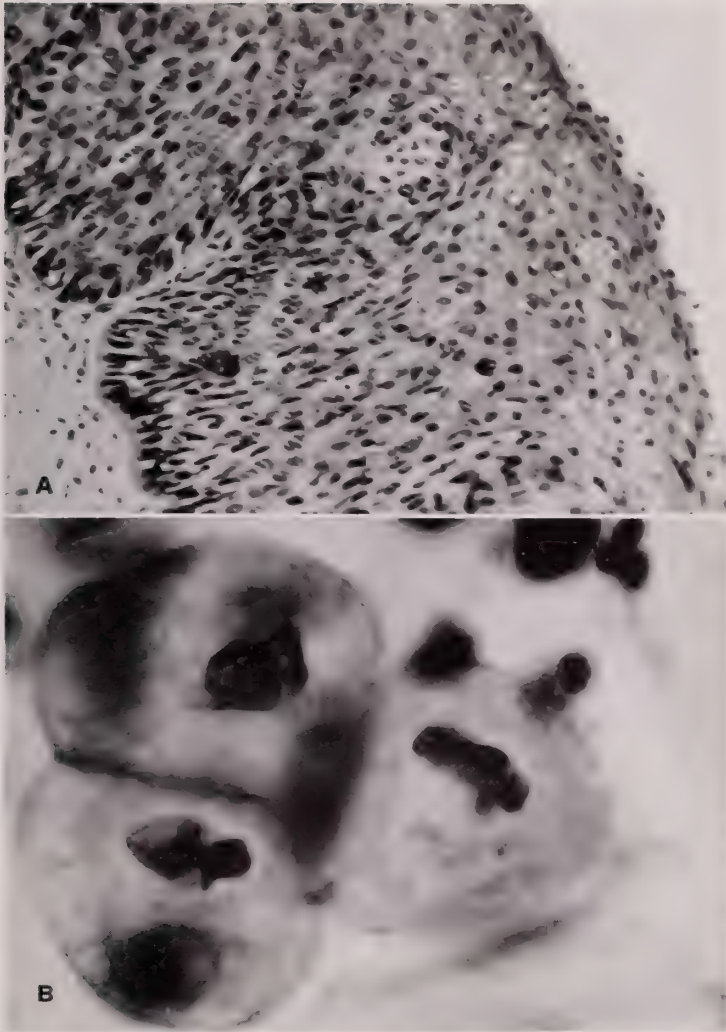


FIG. 6a. Basal spindle cell proliferation with cellular differentiation towards the surface in a case of cervicitis ($\times 125$).

FIG. 6b. Cervical smear with cells from the surface of the same lesion ($\times 1000$).

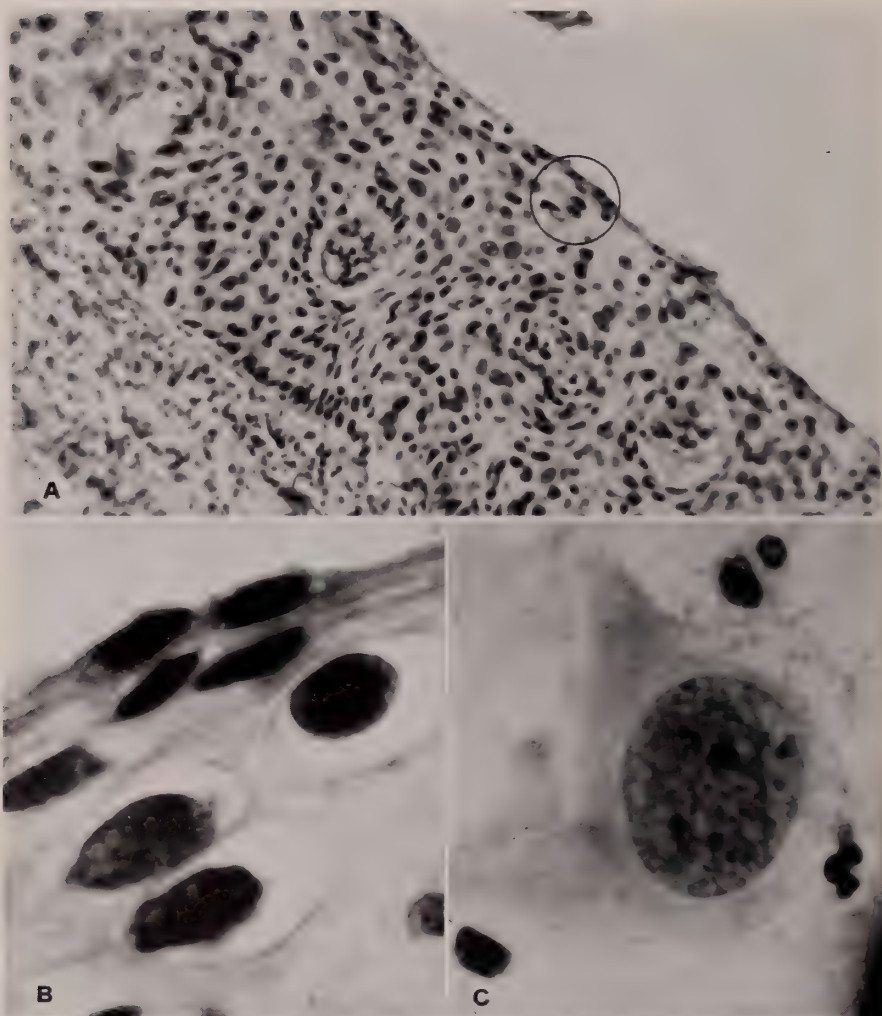


FIG. 7a. Tissue with atypical dysplasia. Note the lack of stratification in some parts of the epithelium ($\times 125$). Invasive carcinoma was found 9 years later.

FIG. 7b. Increased magnification of cells from the surface of the epithelium of Fig. 7a. ($\times 1000$). The nuclear structure in one of the cells consists of numerous distinct chromocenters and bands and was suggestive of a potentially malignant lesion.

FIG. 7c. Cervical smear from the same lesion with a cellular structure essentially identical with that of Fig. 7b ($\times 1000$).

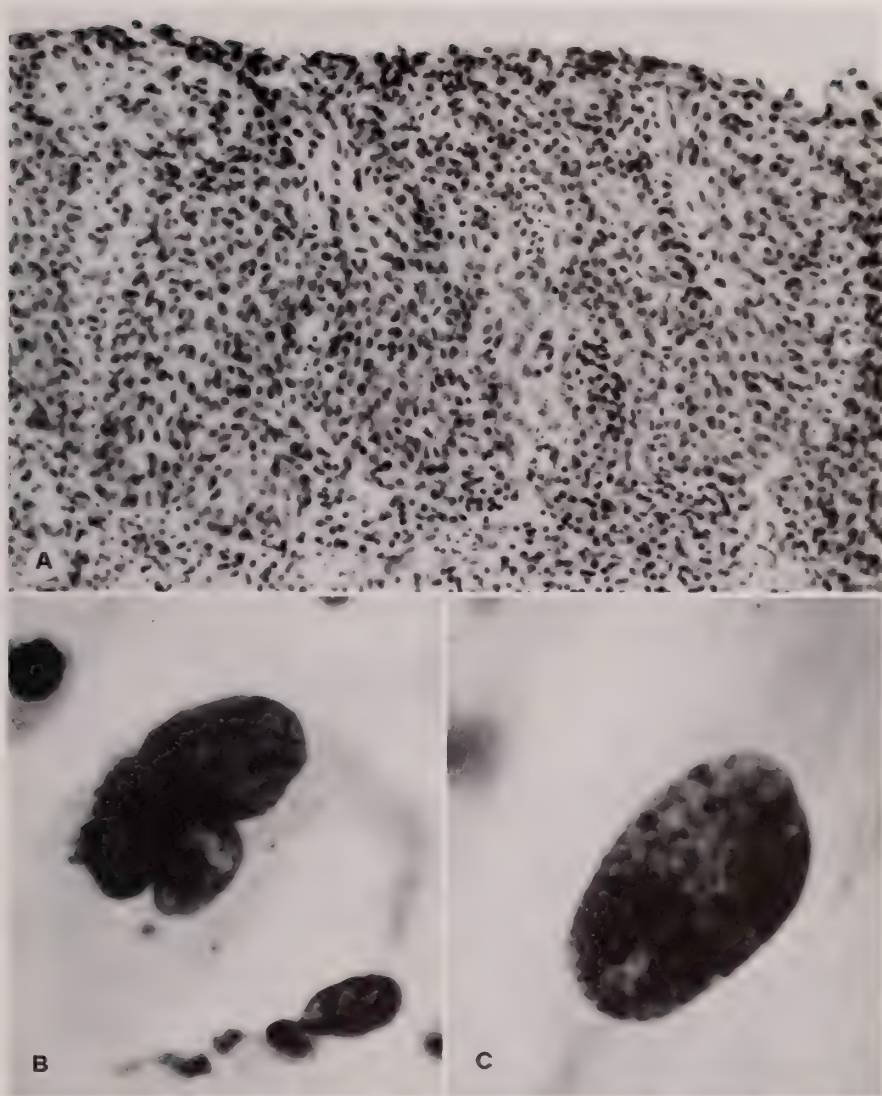


FIG. 8a. Cervical carcinoma with an intact basement membrane. Note loss of stratification and of uniform cellular polarity ($\times 125$).

FIGS. 8b & c. Cervical smear with atypical cells from the same lesion as Fig. 8a ($\times 1000$). The nuclear changes are characteristic for malignant tumor cells. Invasive carcinoma was found in this patient 3 years later.

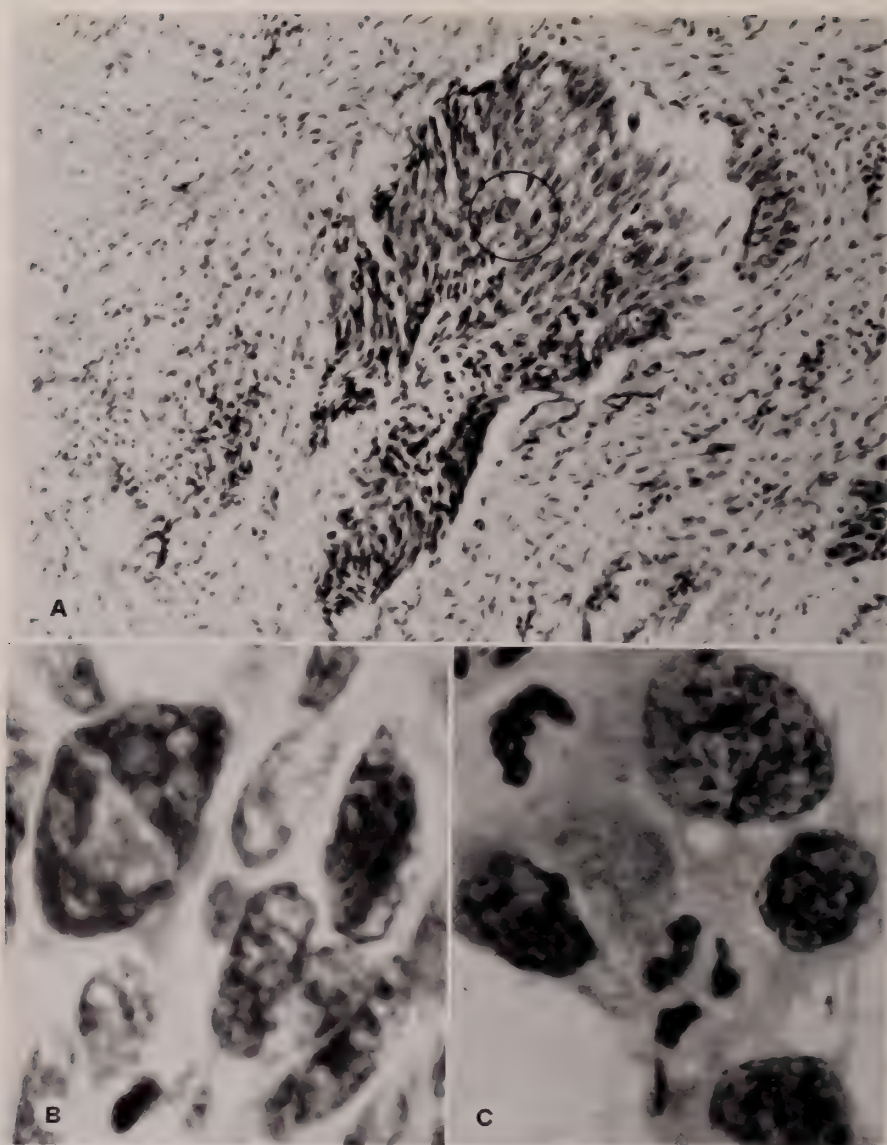


FIG. 9a. Cervical gland with atypical dysplasia ($\times 125$). Minimal infiltration was present in adjacent areas.

FIG. 9b. Higher magnification ($\times 1000$) of cells in area of Fig. 9a. Note spindle cells with nuclear structures suggestive of atypical dysplasia and one cell with a nuclear structure suggestive of carcinoma.

FIG. 9c. Cervical smear from the same lesion with nuclear changes suggestive of carcinoma ($\times 1000$).

Cases in which the morphologic cellular changes in smears and sections are characteristic for malignant tumor cells without stromal infiltration thus require the same consideration as patients with Stage I carcinoma.

The combined morphologic classification of cells in smears and histologic sections permits the differentiation of epithelial dysplasia according to its benign or atypical significance and the distinction between atypical dysplasia and carcinoma with a higher degree of accuracy than with either classification alone.

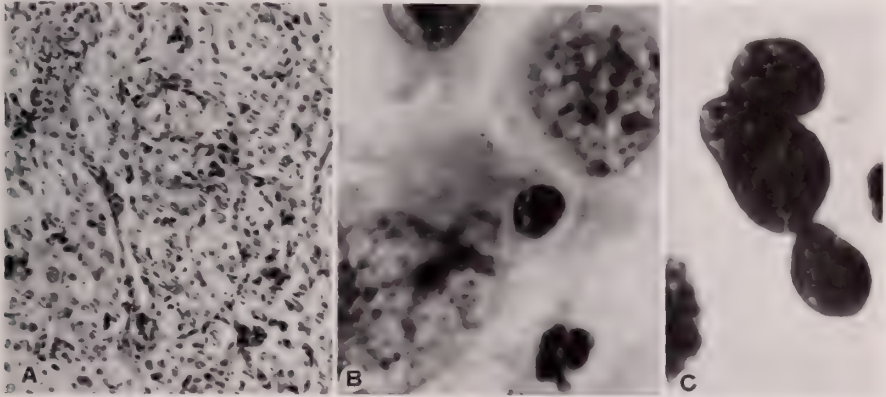


FIG. 10a. Invasive squamous cell carcinoma of the cervix.
FIGS. 10b & c. Malignant tumor cells in cervical smear from the same patient ($\times 1000$).

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AUTOGENIC BLOOD VESSEL GRAFT

AN EXPERIMENTAL STUDY

LESTER BLUM, M.D., AND BERNARD E. HERMAN, M.D.

New York, N.Y.

Growing experience has brought out the complications, early and late, inherent in the use of blood vessel grafts. These include liability to infection, secondary hemorrhage, constriction of the lumen, aneurysm formation, graft degeneration and thrombosis (1-3). In varying degrees, both plastic prosthesis and homograft are susceptible to these sequelae. Both give rise to foreign body reaction in the host. Only where the cellular response is limited to a lamellar arrangement of fibroblastic enveloping tissue, is the result a happy one.

The best available autograft is the saphenous vein (4). In the abdomen, the splenic artery has been employed on the arterial side (5). The difficulty with their use is the technical necessity of much tailoring in order to permit their interposition in large vessel circuits.

In short, each type of graft has its advantages and failings. The ideal would be one of the same composition as the host tissues with size and shape suited to the specific need in each case. This report describes an attempt to approach this desideratum.

In 1936, Mayer and Ransohoff first reported the experimental and clinical use of pure celloidin in the reconstruction of destroyed tendon sheaths in the hand (6-8). The rationale was simply one of inducing a fibroblastic response about a tubular stent of nonreactive material. After some weeks, the ends of the resultant capsule were cut away, the celloidin slipped out and the new tissue cylinder used as a substitute tunnel for the tendon threaded through it.

It would seem logical to attempt application of this procedure to the creation of autogenic substitutes for blood vessels. It is possible that this method may apply to bile duct, dural, urinary bladder and ureteral defects, as well. The initial problem is the establishment of a technique for the constant production of a tissue adaptable to these proposed uses.

Eiken and Norden have reported their experimental method of using preformed autologous connective tissue grafts (polyethylene, polyvinylchloride) in arterial defects (9).

METHOD

Multiple incisions were made into the shaven backs of large (16 to 20 Kg) mongrel dogs under intravenous nembutal anesthesia. The procedures were performed under aseptic conditions. The various materials listed in Table I were placed in subcutaneous pockets away from the lines of incision. At intervals of 106 to 157 days, the dogs were sacrificed and the wound areas ablated *in toto* so as to permit careful examination.

From the Department of Surgery, The Mount Sinai Hospital, New York, N.Y.

In one dog, the cylindrical membrane resulting from a vitallium rod was placed into a defect of the external jugular vein by suture anastomosis (Fig. 1a, 1b).

RESULTS

One wound became infected. This contained the glass tube. Sufficiently severe foreign body reactions to result in extrusion occurred with the iron, wood, and iodinated wooden rods.

Encapsulation with a translucent membrane containing many inflammatory cells was found about the polyethylene tube and steel rod. A few cc of clear fluid were present.

A teflon tube, vitallium and tantalum rods were surrounded by a transparent membrane containing a few drops of limpid fluid (Fig. 2). This membrane could be dissected into an inner lining resembling pleura or peritoneum and a heavier,

TABLE I

Material	Time (days)	Tissue reaction
Glass.....	106	Infected wound
Wood.....	113	
Iodinated wood.....	113	
Iron.....	113	Extruded from wound
Bullet.....	142	
Polyethylene.....	142	Heavy membrane about bullet
Steel.....	157	
Vitallium.....	106	
Tantalum.....	157	Smooth membrane 1-3 cc clear fluid
Teflon.....	157	
		Transparent membrane (2 layers) as a capsule containing few drops of limpid fluid

homogenous, outer coat (Fig. 3). On microscopic section, the capsule is seen to consist of rather dense acellular, fibrous tissue with areas of hyalinization (Fig. 4a, 4b). While no distinct lining is found, a smooth inner surface is formed by fibroblasts aligned in parallel fashion around the lumen.

Dr. Willy Mautner, pathologist, noted that the capsule about the teflon closely resembled that found in the tantalum specimen with three exceptions. First, the teflon envelope was only one-third as thick; second, there were focal areas of chronic inflammatory exudate; and, finally, the inner surface showed areas of marked cellular proliferation which were absent in the tantalum specimen.

Placement of the vitallium capsule into the jugular vein defect was easily performed. The membrane held sutures at least as well as the vein wall and its tensile strength was more than enough to render the procedure an easy, technical performance.

COMMENT

It is evident from these observations that a method is now available for the creation of connective tissue grafts of various sizes and shapes. The cellular



FIG. 1a. Cylindrical membrane (derived from vitallium) being sutured as graft in vein defect.

FIG. 1b. Membrane graft carrying venous blood.



FIG. 2. Teflon tube freed from its membrane.



FIG. 3. Outer layer of membrane dissected from inner layer enveloping teflon tube.

composition can be made to vary by the nature of the stent used to stimulate its formation. Further studies of the physical and biologic characteristics of this autogenic tissue are obviously in order. The response of such a fibroblastic membrane to the varying environment of the cardiovascular tree, biliary and

urinary systems without the complication of antigenic reaction, offers an interesting prospect.

The timetable of tissue formation needs more study. Our results suggest that

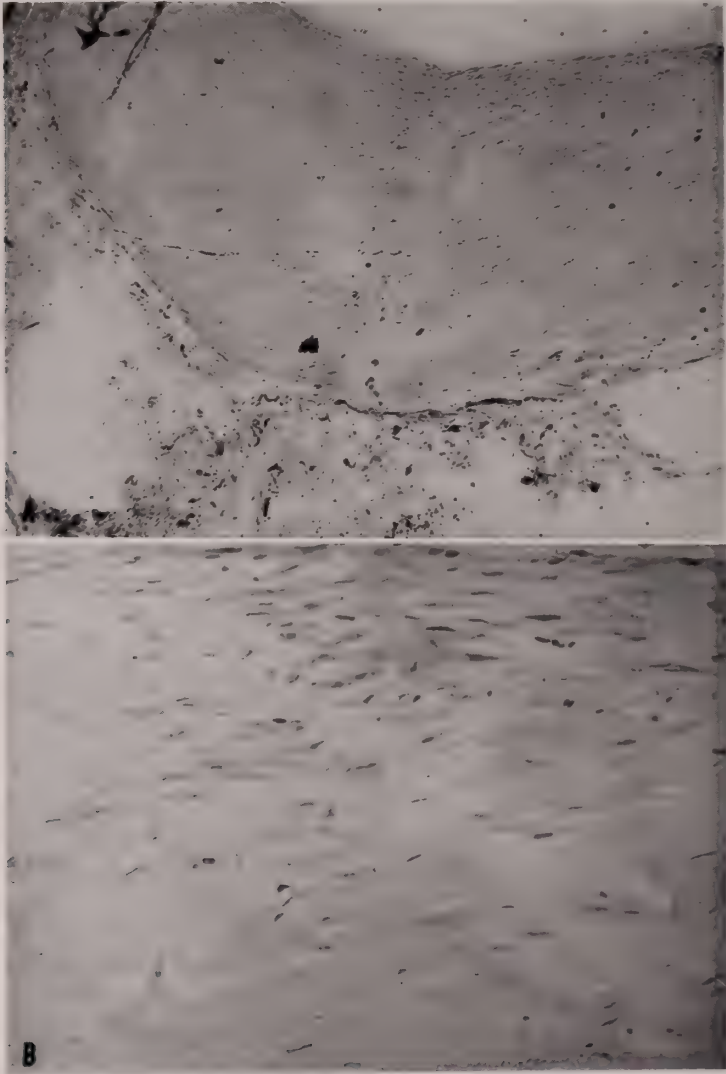


FIG. 4a. Low power section of tantalum envelope showing acellular fibrous tissue.
FIG. 4b. High power view of tantalum capsule showing fibroblasts in parallel about lumen.

the desired effect can be obtained in about one hundred days. It should be unnecessary to add that any type of infection destroys the endeavor.

SUMMARY

A method of producing a smooth sheath of fibroblastic connective tissue in the experimental animal is described.

The cellular and physical characteristics of this tissue suggest its application in bridging defects in blood vessels, bile ducts, urinary bladder and ureter.

The technique permits the formation of autografts of the desired size and shape.

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Clinico-Pathological Conference

POLYARTHRITIS, FEVER AND LATE ONSET OF PULMONARY FINDINGS

Edited by

FENTON SCHAFFNER, M.D.

New York, N.Y.

A 72 year old Negro laborer was admitted to The Mount Sinai Hospital complaining of polyarthritis for two months. It began in the ankles with swelling, pain on motion and morning stiffness. Within a few days his knees and then his hands began to bother him. About the same time he began to notice shortness of breath on exertion. He was seen in an outpatient clinic where he was given pills for his arthritis and for his heart. These produced a 14 pound weight loss and improvement in his symptoms. Because of swelling of his eyelids, he came to the hospital and was found to have a hemoglobin level of 8.0 Gm% for which he was admitted. Past history included a left orchidectomy following scrotal trauma 15 years earlier, and pneumonia many years ago. Careful system review was otherwise completely negative.

On examination his temperature was 100°, pulse 92 min. and blood pressure 128/70. The patient had periorbital edema, mild vascular changes in the optic fundi, poor oral hygiene, postnasal drip, small shotty axillary lymph nodes, and slight enlargement of the heart to the left with a grade II systolic murmur heard over the entire precordium. The lungs were clear, the neck veins were not distended, the liver was not enlarged and no edema was present. The spleen was felt one fingerbreadth below the left costal margin. Crepitation was felt in both knees and fluid was detected in the left one. The fingers and toes showed moderate clubbing.

Urinalyses were repeatedly negative. The hemoglobin was 9.2 Gm% and all electrophoretically type A. The hemoglobin later fluctuated from 7.0 to 10.2 Gm% with the hematocrit ranging from 27 to 31%. The white blood count was 6,050/mm³ and rose as high as 11,600/mm³. Differential counts were normal except for atypical lymphocytes up to 10% and monocytes up to 10%. Sedimentation rate was 100 mm/hr. or higher. BUN, blood sugar, electrolytes, bilirubin, cholesterol, alkaline and acid phosphatase, creatinine, uric acid, transaminase, protein bound iodine, bromsulphalein retention, haptoglobulin and iron binding capacity were all normal although the serum iron was low. Stool guaiacs, Coombs test, tuberculin test, fungal skin tests, LE preparations, blood cultures, febrile and heterophile agglutinins, viral agglutinins, serological tests for trichinosis, Wasserman reaction and Brucella agglutinins were all negative. The bone marrow contained 10% mature plasma cells but was otherwise normal. Serum albumin was 2.0 Gm% and globulin 5.7 Gm%, cephalin flocculation 4+, thymol

From the Department of Pathology, The Mount Sinai Hospital, New York 29, N.Y.

turbidity 12.9 units, C-reactive protein 3+ and latex fixation 1:1280. Paper electrophoresis revealed increased alpha 2 globulin and diffusely increased gamma globulin. White cell alkaline phosphatase was high, a finding consistent with acute inflammation. The synovial fluid in the left knee had 3.3 Gm% protein. A glucose tolerance test was flattened with reduced serum vitamin A and carotene levels and low D-xylose excretion.

X-rays of the hands indicated changes compatible with rheumatoid arthritis. Chest x-ray showed slight enlargement of the heart with some dilatation and tortuosity of the aorta. Barium enema, small bowel studies and intravenous pyelogram were normal. No significant abnormality was seen on an electrocardiogram. A skin and muscle biopsy showed normal skin but vasculitis in the muscle.

The patient remained in the hospital for fifty days, during which time his temperature fluctuated from 99° to 102°. Other joints transiently became hot, swollen and tender. Many groups saw the patient in consultation and no additional findings were elicited. The skin and muscle biopsy site failed to heal. The patient was treated only with salicylates, antacids and iron, with no change in his symptoms or signs. On the 43rd hospital day, ankle and leg edema was noted without dyspnea. Fine inspiratory rales were heard with decreased breath sounds. Chest x-ray revealed diffuse interstitial infiltration in the right lung field and somewhat less on the left side. The aortic knob was noted to be prominent. Fever rose to 102.4° and the patient developed a nonproductive cough. Antibiotics were given without effect. A white blood count was 11,300/mm³ with a left shift, and venous pressure was 90 mm. On the 49th hospital day, he felt weaker and was short of breath, and rales in the chest had increased although his pulse rate was never over 100 /min. An electrocardiogram showed only a few premature atrial contractions but was otherwise unchanged. Early on the morning of the 50th day, he became restless and hypotensive, and expired quickly.

*Dr. Louis E. Siltzbach**: In trying to put this together, I think this man probably had rheumatoid arthritis. He had the typical findings of migratory red hot joints and a latex fixation of 1:1208. He also had certain protein changes including elevation of his serum globulins which are part of the phase reaction in rheumatoid arthritis and one could perhaps also explain the anemia by rheumatoid arthritis as well. He had many negative findings. The x-ray of the hands was thought to be consistent with this diagnosis. However, this leaves much to be elucidated because it is a little difficult to explain the periorbital edema with no albumin in the urine. The absence of hepatomegaly rules out the possibility of superimposed amyloid, which could have explained the malabsorption syndrome. I wonder, though, about secondary amyloidosis, if we put quotes around the word "secondary," in rheumatoid arthritis of this short duration. I would think it unlikely. Rather, it would have to be a chronic, deforming rheumatoid arthritis that would permit enough amyloid to be deposited in the bowel to produce a malabsorption syndrome, and at the same time keep the patient free of any alimentary difficulty, as in this patient.

* Attending Physician for Thoracic Diseases, The Mount Sinai Hospital, New York.

We know that brucellosis can produce joint difficulties. A brucella agglutination test was negative, and we have no reason to believe that this man had brucellosis.

In a Negro of seventy years of age, who has a febrile disease, one must always think of superimposed miliary tuberculosis. We do not find any evidence of this in the x-ray films but we know that people still die with miliary tuberculosis. This man had a negative tuberculin test, but that does not rule it out, because patients may lose their tuberculin sensitivity when they die of miliary tuberculosis. However, there is not really very much to support this diagnosis in any other way. He did not have, for example, steroid therapy which might have caused a flare-up of inactive tuberculosis.

One diagnosis that suggested itself is that very elusive concept of Poncet's rheumatism, or tuberculosis with a rheumatoid-like picture. I believe that perhaps these are patients with tuberculosis who also had rheumatoid arthritis. We did not have the latex fixation test in those days to help us with the diagnosis.

This man had some heart failure terminally which could be very well explained by arteriosclerotic heart disease, and I am really left with a single diagnosis of rheumatoid arthritis. I shall endeavor to invoke this etiology to explain the findings in the lung on that basis.

In looking at these lungs, we find interstitial infiltrations which occurred while the patient was under observation. Of all the interstitial infiltrations which lead to such a quick termination, the rheumatoid ones are described as occurring latest in the disease. Those people who believe that there is such a thing as rheumatoid changes in the lung, and I am one of them, have seen that this comes late in the disease. Three manifestations interest us in this condition, and two of them are absent here. More and more we see right and left pleural effusions in patients with rheumatoid arthritis. This is very useful in differentiating such cases from those with the Hamman-Rich syndrome, because in the Hamman-Rich syndrome one does not have pleural effusions except in the very terminal state, as a result of heart failure. Where the lesions of rheumatoid arthritis were found in the lung, pleural effusions were noted in as high as fifty per cent of such cases. These pleural effusions are rather interesting. They are exudates, and for some reason that is not clear, they have a low sugar content and a fairly high protein content, which reminds one of the pleural effusions of tuberculosis. Pleural effusion is one manifestation that is absent here.

The second manifestation, which is much less common, is the development of nodules in the lung. These nodules are the pulmonary representation of what one finds in the subcutaneous tissues. They have a rather characteristic histologic appearance with a center of eosinophilic staining fibrinoid surrounded by histiocytes and lymphocytes. Cavities are also found in some patients but not often in this country. We find them more frequently, however, in patients who have been exposed to industrial dusts, anthracosis and silicosis. It is called Caplan's syndrome, after the man who first described it, and is a condition in which the patient may have evidence of rheumatoid arthritis and silicosis (1).

Caplan noted that some patients with nodules in the lungs, which he thought were tuberculous, had rheumatoid arthritis. While it occurs in this country, it has not been found as frequently as Gough and his associates in Wales have described it (2).

The last manifestation of rheumatoid disease of the lung is interstitial fibrosis. When Hamman and Rich first described acute idiopathic interstitial fibrosis (3), three out of their four cases occurred very acutely. We do not see as much acute Hamman-Rich syndrome now as we did in the past. Our explanation is that perhaps these patients really had chronic interstitial infiltrations and what we saw were acute and terminal manifestations of the chronic condition. I do not think that is quite the same situation in rheumatoid lung disease which I consider to be somewhat more fluctuating and not so inexorable as the Hamman-Rich syndrome. The interstitial changes in rheumatoid arthritis seem to me to be much more responsive to steroids. Radiologic resolution occurs much more readily in that type of patient than it does in the Hamman-Rich syndrome, where the response is quite poor.

Therefore, the third manifestation, and this is the one perhaps we should be thinking of most here, has occurred in a man who during the course of rheumatoid arthritis has laid down abnormal interstitium of his lung characterized usually by some fibrinoid deposits and by some vasculitis. This condition incidentally may have been mirrored in this man's muscles because he also had a vasculitis there. Vascular lesions in rheumatoid arthritis have been found in a fair number of patients. However, when one takes into account the huge number of patients with rheumatoid arthritis, the incidence of these vascular lesions is not great.

I do not understand what caused the patient's edema but I think it is not very important. I do not quite understand what caused the malabsorption syndrome, which is more important. Malabsorption cannot be ascribed to vasculitis in the bowel secondary to the arteritis of rheumatoid arthritis. I would have expected that such a patient would have blood in his stool and would have some bowel difficulty.

*Dr. Alexander B. Gutman**: What bothered me was the short duration of the rheumatoid arthritis which developed two months prior to admission to the hospital and which apparently was the first indication of any polyarthritis. To imagine that so much disease developed associated with rheumatoid arthritis is difficult.

I also was puzzled by a serum globulin of 5.7 Gm% which is very high. To be sure, hyperglobulinemia occurs in rheumatoid arthritis, but usually late, when there are severe and permanent changes. The only severe joint manifestation that he had was in the right knee, which was crepitant, and I thought it was probably as much due to osteoarthritis as to rheumatoid arthritis. The alternative possibility which you have considered, namely, that he began with pulmonary disease, even though this is not very evident in the x-ray films, and then the kind of arthritis that one sees associated with chronic interstitial fibrosis

* Director, Department of Medicine, The Mount Sinai Hospital, New York.

developed, would presume that he had pulmonary fibrosis much longer than he had symptoms. Perhaps his emphysema is an indication of just that.

Dr. Siltzbach: I was troubled by the very rapid onset and the termination of his illness. The high globulin also bothered me but I decided that I had no alternative explanation.

Actually, the differentiation between acute Hamman-Rich syndrome with joint manifestations and rheumatoid arthritis is extremely difficult. We have recently studied 25 cases of Hamman-Rich disease and we never saw one quite like this. All of our cases had a negative latex fixation test and this man, as you know, had a titer of 1:1280. I may be putting too much stress on that finding, but I think it is rather significant.

The relation of Hamman-Rich syndrome to joint pains is one which is quite troubling because about one-fourth of patients with what we call chronic interstitial idiopathic pulmonary fibrosis do get joint pains. They also have clubbing, which this man had. However, I am unwilling to say that this was a classical Hamman-Rich syndrome with joint pains, primarily because I have never seen this type of rapid development from normal appearing lungs, joint pains or no joint pains. I would think, too, that emphysema would not be a particular indication of interstitial fibrosis because in general patients who have had idiopathic interstitial fibrosis for any length of time miniaturize their lungs rather than expand them. They have all the restrictive phenomena rather than blocking of bronchioles to account for respiratory difficulty.

Dr. Gutman: I would like to make one other comment. The serum albumin was extremely low, 2 Gm%. This was not due to loss in the urine, which would be expected if amyloidosis were present. I find it hard to explain the absorptive difficulty on the basis of amyloidosis. However, an exudative enteropathy seems to be a possible avenue of loss of protein. Hypoalbuminemia might very well account for the periorbital edema which persisted. I do not know how to relate it to the other diseases that he had. The only other possibility is that he had liver disease. There was never any evidence of cirrhosis to account for the hypoalbuminemia and the hyperglobulinemia.

Dr. Siltzbach: A gastrointestinal series did not show any abnormality. I do not know whether one can lose a lot of albumin through the gut and not have any bowel symptoms at all.

Dr. Gutman: There can be severe loss of proteins through the gut, which can produce hypoalbuminemia with no clinical roentgenological evidences in intestinal disease.

Question: Dr. Gutman, has that not been described in Sjögren's syndrome, in which rheumatoid arthritis frequently occurs?

Dr. Gutman: Yes. In this disease excess 19S macroglobulin is in the circulation and it has been suggested that this forms a sludge which is caught in the capillaries of the lung and produces pulmonary fibrosis. While this seems a little naïve and would have to involve very small capillaries, if the macroglobulin did tend to precipitate, it is conceivable that it would occur in the lungs, where the circulation time may be a little slower. Unfortunately, the gamma globulin is de-

scribed on electrophoresis as diffusely increased and did not show a peak to suggest that excess macroglobulins were present. They were present, however, because they produced the high latex fixation titer.

*Dr. Emanuel Rubin**: I would like to thank Dr. Siltzbach and Dr. Gutman

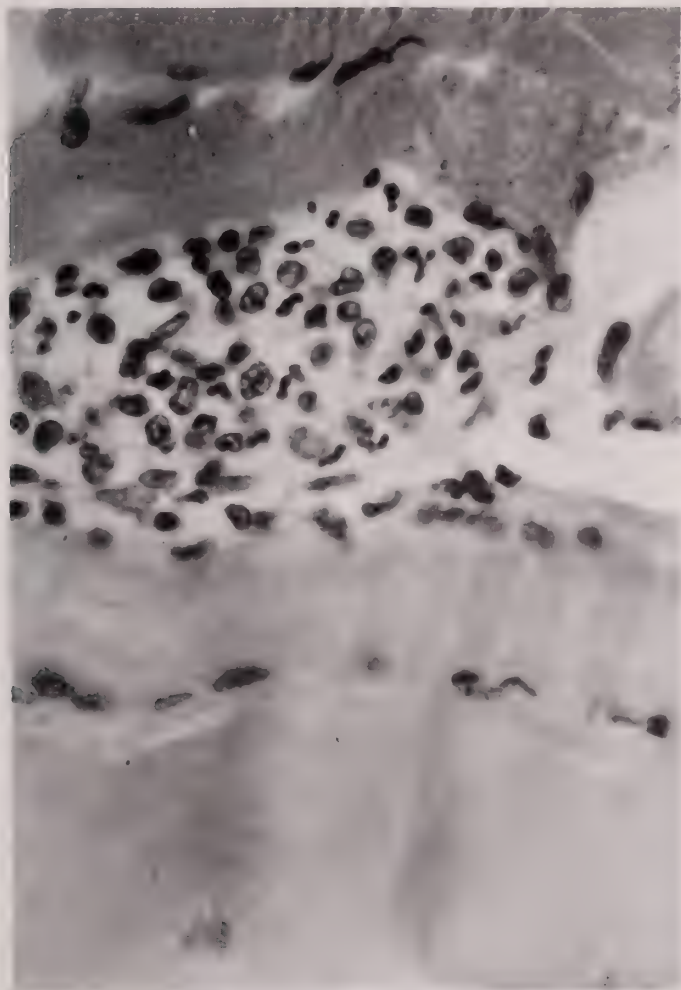


FIG. 1. Section of muscle showing focus of inflammatory cells. Hematoxylin-eosin $\times 450$

for an illuminating discussion that I feel does full justice to the very interesting pathology of this case.

In the muscle biopsy, a vessel was seen with a smudgy wall and a few inflammatory cells around it. This was reported as a vasculitis, but was entirely non-specific. At autopsy we found an arteritis in many muscles, with many plasma cells around the vessels. Also diffusely spread throughout the muscles were many

* Assistant Attending Pathologist, The Mount Sinai Hospital, New York.

inflammatory cells, including numerous polymorphonuclear leukocytes, indicating an acute myositis (Fig. 1). We also found numerous macrophages, indicating that this myositis was probably present for some time, but was still an active process.

In the knee joint we saw vascularization and numerous inflammatory cells scattered throughout. On closer inspection, most of them were classic plasma cells. We wondered whether this was rheumatoid arthritis, and in order to solve this problem we turned to our immunocytochemist, Dr. Koffler, who very kindly examined several sections using the fluoresceinated antibody technique. Using fluoresceinated antimacroglobulin, many of the plasma cells were shown to contain macroglobulin (Fig. 2). We believe that this corresponds to the latex fixation factor which was found clinically. Thus, I think we can definitely say that this man had rheumatoid arthritis.

The spleen was about twice the normal size and was moderately soft. It also contained large numbers of plasma cells, some of which were large and polyploid. Macroglobulin was demonstrated in some of these cells while others contained normal 7S gamma globulin.

Many plasma cells were scattered throughout the lymph nodes, where they appeared to be the predominant cell type. We found these cells also elaborating the same abnormal protein which we relate to the rheumatoid factor. There was also a diffuse plasmacytosis in the bone marrow.

This man, then, had rheumatoid arthritis with a generalized plasmacytosis, and increased production of both gamma globulins and macroglobulins.

When we examined the kidneys, both were enlarged, the left weighing 210 grams and the right 260 grams. There was an early membranous glomerulitis, which apparently was not important clinically, since no albumin was found in the urine. However, we did find an active interstitial nephritis with many inflammatory cells, most of which were plasma cells.

While the heart was only moderately enlarged on x-ray, it weighed 610 grams, which is about twice normal. Both ventricles were hypertrophied. We wondered what could account for this tremendous hypertrophy in the absence of hypertension. We found a diffuse fibrosis of the myocardium, which could have been ischemic in origin, as the result of arteriosclerotic heart disease (Fig. 3). This fibrosis was diffusely spread throughout the myocardium, surrounding myocardial fibers. However, the coronary arteries were entirely normal. Nowhere was there any narrowing or occlusion. However, we did find various stages of myocarditis (Fig. 4), from acute necrosis with numerous plasma cells and mononuclear cells, to early fibrosis where the myocardial fibers had disappeared, to still older stages with fibroblasts and a more advanced organization of the affected areas. Thus, we have acute and chronic myocarditis with diffuse myocardial fibrosis.

We found old arteritis in the heart which was evidence of a process which had been going on for a considerable time before the onset of any symptoms. Pericarditis in which numerous plasma cells participated was also present.

The lungs were very large, the right lung weighing 1300 grams and the left

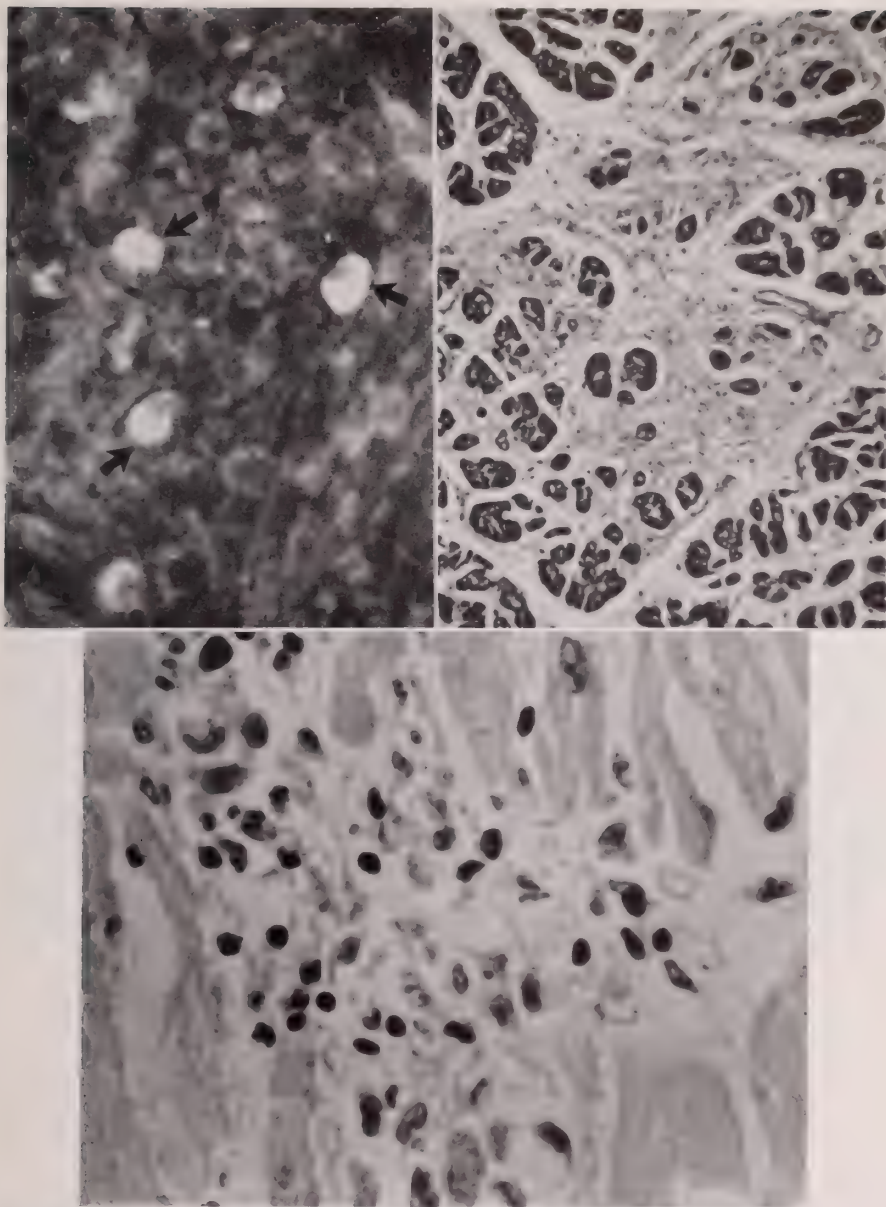


FIG. 2. Fluorescence photomicrograph of section of synovial membrane after treatment with fluoresceinated antimacroglobulin. Fluorescent cells (arrows) are plasma cells containing macroglobulin $\times 600$.

FIG. 3. Section of heart showing myocardial fibrosis. Chromotrope aniline blue $\times 150$.

FIG. 4. Section of myocardium showing myocarditis. Hematoxylin-eosin $\times 450$.

1100 grams. It would be unusual to find this solely on the basis of pulmonary edema.

Microscopically, there was diffuse fibrosis throughout the lungs, but the fibrosis was entirely interstitial (Fig. 5). The alveoli were somewhat enlarged, and the alveolar epithelium which is usually very flat was changed to a columnar type (Fig. 6). The septa were diffusely thickened due to an increase in reticulum fibers.

In other areas there was organization within alveoli in addition to the purely interstitial fibrosis. In some places there was merging or consolidation of the

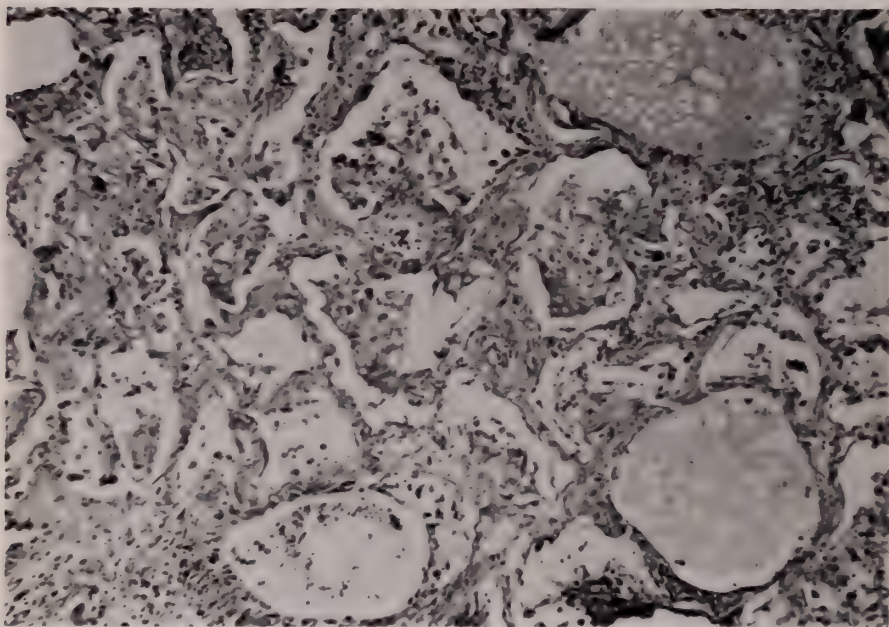


FIG. 5. Section of lung showing diffuse interstitial fibrosis. Chromotrope aniline blue $\times 150$.

fibrotic areas so that these areas were almost completely airless and replaced by fibrous tissue. In the septa we found a pronounced inflammatory reaction characterized by the same plasma cells that were seen in other organs (Fig. 7). In other areas we saw typical fibroblasts proliferating within the interstitial septa. Active phagocytes, containing PAS positive material, were also present. Thus the lung revealed cells which were producing protein, cells forming fibers, and cells acting as phagocytes, indicating that all the elements of the mesenchyma had become hyperactive in the lung. In areas the process was considerably older and relatively hypocellular.

I think we can safely say that these changes must have antedated the acute onset of symptoms and radiologic findings which were evident in the clinical history. In some areas large emphysematous alveoli were filled with a peculiar protein-rich edema fluid, which in some areas was coagulated along the borders

of the alveoli in the form of a hyaline membrane. The pulmonary artery branches showed reduplication of the elastic fibers and intimal proliferation and fibrosis indicative of early pulmonary hypertension.

I do not know whether the cardiac hypertrophy and fibrosis were solely on the basis of myocarditis. You may remember that Dr. Zak recently presented a case of a young Negro man with rheumatoid arthritis who also had an enlarged

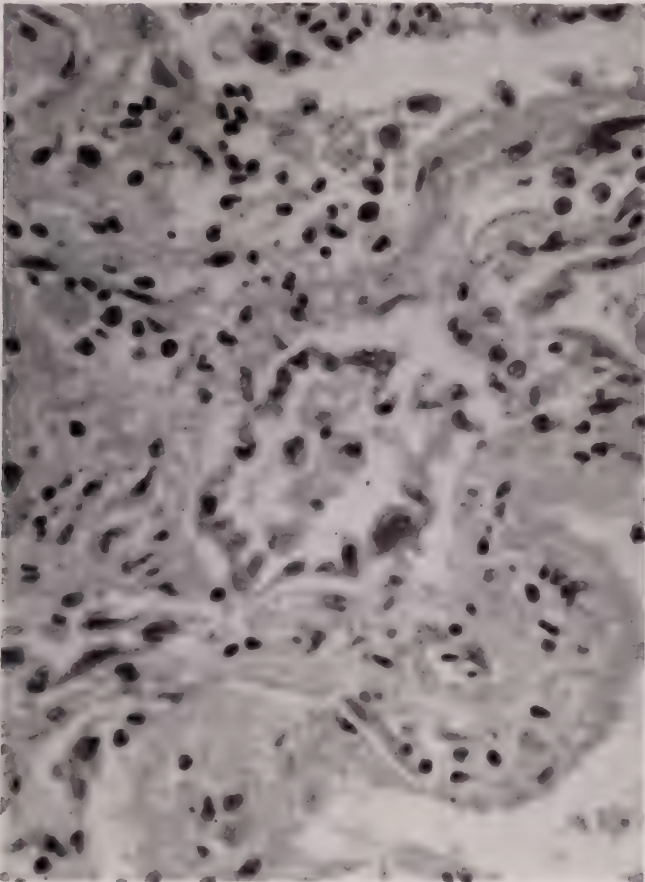


FIG. 6. Section of lung showing columnar alveolar epithelium. Hematoxylin-eosin $\times 240$.

heart with no apparent cause (4). This was categorized as idiopathic cardiac hypertrophy in the presence of rheumatoid arthritis, or cardiac hypertrophy of unknown cause. Here is a second case of a Negro man with rheumatoid arthritis who also had a large heart.

The lung was definitely the site of acute diffuse interstitial fibrosis. Nowhere were there any rheumatoid nodules. Nowhere was there necrosis or palisading, and I cannot relate these morphologic findings to any specific disease. It resembles the diffuse interstitial fibrosis found in scleroderma or lupus erythematosus

or after viral pneumonias. The intestinal tract here was morphologically normal. We were unable to demonstrate any disease of the intestine. At postmortem autolytic changes of the intestinal mucosa are often severe, and the subtle changes of sprue or other malabsorptive syndromes are not always evident.

This was a generalized disease and was associated with acute diffuse interstitial fibrosis of the lung. I think it is entirely correct to call this the Hamman-Rich syndrome if we relate it to the original cases described by Hamman and Rich. In the original four cases, the longest survival was six months and one patient died one month after the onset of the symptoms.

This patient probably had congestive failure on the basis of cardiac hyper-

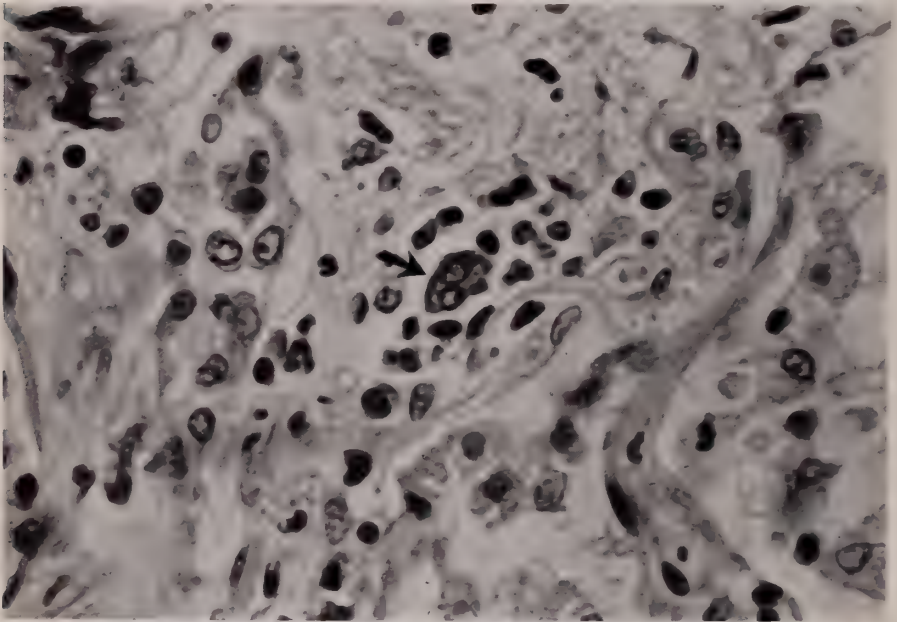


FIG. 7. Section of lung showing inflammatory reaction composed of plasma cells, macrophages and fibroblasts. Note polyploid plasma cell (arrow).

trophy and myocarditis, which added to his troubles. He had an interstitial nephritis and had he lived longer, he probably would have had renal symptoms.

An associated finding, which was not clinically noteworthy, was generalized myositis. He also had a generalized plasmacytosis, these plasma cells producing increased gamma globulin and macroglobulins which were responsible for the positive latex fixation.

In summary, while this patient had rheumatoid arthritis, I think it would be incorrect to label the over-all disease rheumatoid arthritis, because the arthritis was one of its minor manifestations and certainly had no effect on the clinical course. I would prefer the term generalized rheumatoid disease.

We are fortunate in having with us Dr. Eli Rubin, no relation of mine, who has written extensively on diseases of the chest and particularly on diffuse inter-

stitial fibrosis of the lung associated with rheumatoid disease (5). I should like to call on him for any comments he would like to make.

*Dr. Eli H. Rubin**: To me the important thing is that two relatively infrequent syndromes, rheumatoid disease and the Hamman-Rich syndrome, were combined in a patient who also had plasmacytosis. When several syndromes occur together in a single patient, it is much more instructive than studying dozens of cases from a statistical point of view.

When I became interested in rheumatoid lung disease, I was impressed by the lung findings obtained by lung biopsy which were indistinguishable from those in the Hamman-Rich syndrome. My major interest has been the correlation of clinical symptoms and signs and x-ray and lung findings in the two diseases.

Some of the patients with the Hamman-Rich syndrome also had rheumatoid symptoms and they presented a combination of both diseases that was very intriguing. The question arose whether certain forms of the Hamman-Rich syndrome were frustrated forms of rheumatoid disease which may have been generalized at one time but attacked the lung chiefly. We have this analogy in other types of collagen diseases. Subsequently the idea was advanced that certain forms of the Hamman-Rich syndrome, particularly the acute type, were related to the pulmonary changes in rheumatoid arthritis.

It is very rare that we find the granulomas of rheumatoid arthritis within the lung or in the pleura. They have been described in only five or six cases, as Dr. Siltzbach mentioned. Diffuse interstitial fibrosis and pleural effusions have been found. Both of these are nonspecific. In this instance, occurring together with plasmacytosis, it may indicate an immunological background of both syndromes. Except for one similar case in the French literature of a young girl (6), I do not think there has been a case reported just of this type that is so instructive.

Dr. Emanuel Rubin: Thank you, Dr. Rubin. I would like to add two things. Most cases in the literature are rheumatoid arthritis or rheumatoid disease of relatively short duration. Few have rheumatoid arthritis for many years with a sudden superimposed diffuse interstitial fibrosis.

The second point is that in a paper by Sinclair and Cruikshank on the visceral manifestations of rheumatoid arthritis (7), which they then called rheumatoid disease, of 16 cases five had a myocarditis, and in three the myocarditis was considered to be the cause of death. It is important to think of myocarditis as an important feature of this disease.

Dr. Siltzbach: One can get a distorted impression of the relationship of rheumatoid arthritis and Hamman-Rich disease if one joins the group of lumpers who are now putting all of the so-called collagen diseases together. Rather, I belong to the group of splitters. I still think that it is important to try to keep these diseases, if at all possible, discrete from the other. Between the circle of the patients with rheumatoid arthritis and the very much smaller circle of patients with Hamman-Rich syndrome, there will be a penumbra, and we will have

* Attending Physician, Division of Pulmonary Medicine, Montefiore Hospital, New York

difficulties in trying to decide into which group one fits. One of the important points in making the diagnosis of Hamman-Rich syndrome is the fact that at autopsy there is no evidence of generalized disease. Most patients fit this category, and I prefer, at the moment to try to keep these cases apart.

This present case is another good object lesson in attempting to correlate what is found in the x-ray and terminally what was found at autopsy.

Dr. Gutman raised the question of how we know that the emphysema was not due to interstitial fibrosis, and I answered rather glibly that patients with interstitial fibrosis usually do not have the x-ray type of picture. The older and thicker fibers were not seen, primarily because there was so much normal lung for the x-rays to pass through. When there are little septa or little strands in the lung at autopsy, as we saw in this case, films must read as being within normal limits for a 70 year old man.

Dr. Eli H. Rubin: I would like to make one additional comment about the Hamman-Rich syndrome and rheumatoid disease. I recall a patient with systemic lupus erythematosus who had a great deal of steroid treatment and needed oxygen continuously. The patient died and at autopsy the only significant finding was diffuse interstitial pulmonary fibrosis like that seen in the Hamman-Rich syndrome, without any other evidence of systemic lesions. All the transient phenomena that had occurred during life in the patient with a well-documented systemic disease had disappeared. Therefore, when we see a patient with the Hamman-Rich syndrome it does not necessarily mean that it is a primary disease localized in the lungs. We also have the analogy in other conditions. I think that a number of patients with Hamman-Rich syndrome represent the pulmonary manifestations of a systemic disease about which we know little.

Dr. Emanuel Rubin: I think that the similarity of the histological appearance of the lungs, the heart, the joints and the kidneys would suggest a common etiology for all, but the question is unanswered.

Final diagnosis: RHEUMATOID DISEASE WITH: ACUTE DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS (HAMMAN-RICH SYNDROME); MYOCARDITIS, ACUTE AND CHRONIC; INTERSTITIAL NEPHRITIS; RHEUMATOID ARTHRITIS; MYOSITIS, GENERALIZED; AND PLASMACYTOSIS, GENERALIZED.

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Radiological Notes

CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D., Co-EDITORS

New York, N. Y.

CASE NO. 185

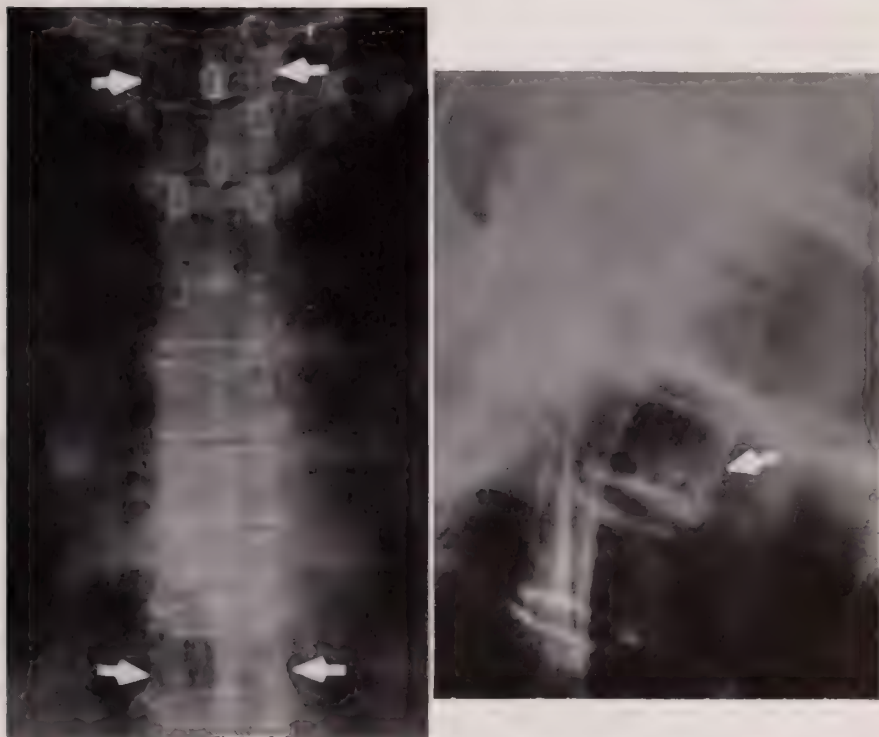
A forty-nine year old female was admitted to the hospital with a three-month history of pain in the midback radiating down both legs and increasing weakness in the lower extremities. The patient related her symptoms to a fall at which time she hurt her left arm and twisted her back. Past history revealed no contributory data. General physical examination was within normal limits. Neurologic examination revealed early paraparesis of the lower extremities with hyperreflexia, bilateral Babinski signs, but no sensory level. Lumbar puncture revealed normal pressure and manometries; routine laboratory tests of spinal fluid were normal. A spinal cord abnormality was suspected and conventional radiographic examination of the spine as well as myelography were performed.



Case 185. Fig. 1. Antero-posterior film of the dorsal spine made 10 years prior to admission shows a small zone of irregular lucency creating a coarsened trabecular pattern in the left half of the body of D2 (arrow). D9 is normal at this time.

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

Conventional films of the dorsal spine showed an extensive honeycombed appearance to the trabecular pattern of the entire body of D2 (Fig. 2A and 2B). The anterior portion of the left side of the neural arch and the left transverse process were also involved. The body of D9 showed a similar but less extensive process. The diagnosis of hemangioma of D2 and D9 was advanced. Films of the dorsal spine made ten years prior to admission were reviewed and revealed



Case 185. Fig. 2. A. Antero-posterior film of the dorsal spine made during the current admission shows an extensive honeycombed appearance to the trabecular pattern of the entire body of D2 (upper arrows). The body of D9 shows a similar but less extensive process (lower arrows).

Case 185. Fig. 2. B. Lateral view of D2 at the same time also reveals the changes in the vertebral body.

a small zone of coarsened trabecular pattern in the left half of the body of D2 (Fig. 1). It was felt that the hemangioma of bone was present at that time and had increased considerably in extent in the intervening period. The body of D9 was normal. (The indication for the original examination is not known.)

Myelography was performed with introduction of opaque material via the lumbar route. A complete block of the cephalad flow of opaque material was encountered at the D2-3 level with the patient in the head-down position. The appearance of the block was characteristic of an extradural lesion. The diagnosis of epidural involvement from a hemangioma of bone was advanced.

A laminectomy was performed extending from C7 to D3. The bone of D2 was noted to be softened and infiltrated by a highly vascularized process. The epidural space was filled with extremely vascular tissue apparently extending from the adjacent bone. The bone itself was described by the surgeon as "cardboard-like" in consistency. A gross total removal of all abnormal epidural tissue was accomplished. Histologic examination of the tissue removed revealed the characteristic pattern of cavernous hemangioma.

Postoperatively, the patient gradually recovered all function in her lower extremities and neurologic examination became normal. A course of radiotherapy directed toward the area of involvement was completed uneventfully. When seen one year following discharge, the patient complained of occasional pain in the upper back adjacent to the incision but there were no abnormal neurologic findings.

Case Report: VERTEBRAL HEMANGIOMA OF DORSAL SPINE WITH SPINAL CORD COMPRESSION.

See discussion, Case No. 186.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Ralph Greenberg and A. Z. Freudenheim, Good Samaritan Hospital, Suffern, New York.

CASE NO. 186

A twenty-nine year old female was admitted to the hospital with a chief complaint of weakness and loss of sensation in both lower extremities. The patient was in the eighth month of pregnancy. Two and one-half months prior to admission she noticed the gradual onset of progressive weakness in both lower extremities. Two weeks prior to admission pain was experienced between the shoulder blades and this gradually increased to a girdle-like tightness around the upper part of the abdomen and lower chest. Paresthesias of the lower extremities became prominent, and finally there was no sensation in the lower extremities at the time of admission. The patient also described urgency of urination and slight incontinence.

On examination the patient was unable to walk. A third trimester pregnancy was confirmed. Neurologic examination revealed a severe spastic paraparesis with a sensory level in the mid-dorsal region.

Conventional radiographs of the dorsal spine revealed a coarsened and honey-combed trabecular pattern throughout the body of D7, characteristic of hemangioma (Fig. 1A and 1B). The pedicles were also involved. Myelography was performed with opaque material introduced via the lumbar route. There was a complete block to the cephalad flow of opaque material at the lower margin of D7 with a configuration indicative of an extradural process. A small left paraspinous soft tissue mass was also noted.

A dorsal laminectomy was performed extending from D6 to D8. The spinal cord was displaced dorsally. The ventral aspect of the cord was not investigated. The cord was thoroughly decompressed and the dura left opened.

Postoperatively, a complete spastic paraplegia developed. Although caesar-

ian section was contemplated, a spontaneous delivery of a normal premature infant occurred. The patient then received a full course of radiotherapy to the region of the diseased vertebra, and vigorous physiotherapy was instituted. The spastic paraplegia did not improve, although bladder and bowel function became normal. The patient was transferred to a rehabilitation center for further therapy.

DISCUSSION

Vertebral hemangioma is a common abnormality which is demonstrable radiographically when it attains sufficient size. Several autopsy series searching specifically for this abnormality revealed an incidence of 10 to 12 per cent



Case 186. Fig. 1A. Antero-posterior view of the dorsal spine shows a complete block to the cephalad flow of opaque material at the lower margin of D7. The configuration is that of an extradural process. The trabecular pattern throughout the body of D7 is coarsened and honeycombed in appearance. The pedicles are poorly seen, indicating involvement by a similar process. A left paraspinal mass is noted (arrow A). An opaque marker to the left of the spine is on the skin for localization purposes.

Case 186. Fig. 1B. Lateral view shows expansion of the pedicles (between arrows) and loss of the contour of the posterior aspect of the vertebral body. The coarsened trabecular pattern is again demonstrated.

(1, 2), but these figures include many lesions which were very small or microscopic in size and not demonstrable by ordinary radiographic techniques. The dorsal spine from D3 to D10 is most often involved, and multiple lesions are not infrequent. The hemangioma is almost invariably of the cavernous variety. It is benign and nonmetastasizing but is capable of growth. Ordinarily, its discovery represents an incidental finding. That the lesion can give rise to local symptoms and severe neurologic complications is often not appreciated.

Although Virchow is credited with mentioning a patient with "myelogenous telangiectasis" (3), Gerhardt described the first well-documented case of vertebral hemangioma with paraplegia in 1895 (4). Perman described the classic radiographic appearance of vertebral hemangioma in 1927 (5). Numerous case reports and reviews have appeared in the more recent literature (6-8).

The radiographic findings reflect the pathologic change of vascular structures

replacing and distorting the normal bony architecture. The normal trabecular pattern is transformed into a coarse meshwork. The bone appears porous by virtue of small, variably sized, well-defined lucent zones. The remaining trabeculae are often thickened and may be vertically oriented giving rise to a striated appearance. While the vertebral body itself is most often involved, the lesion can extend into or appear *de novo* in the neural arch and its appendages. The bone may be expanded or ballooned by the process or collapse may result from mechanical stress. Intraspinal or paraspinal extensions may occur. The characteristic radiographic appearance is virtually pathognomonic. Whereas myeloma, lymphoma, and metastatic malignant disease may be mentioned in passing in the differential diagnosis, these entities will rarely be confusing in the differential diagnosis, these entities will rarely be confusing in the absence of significant vertebral collapse.

Neurologic complications are due to nerve root or spinal cord compression. They occur as a result of vertebral collapse or encroachment on the spinal canal or intervertebral foramina by expanded bone or contiguous soft tissue mass. There appears to be an increased incidence of complications during pregnancy; hypothesis of venous engorgement and hormonal influence on the growth of smooth muscle have been advanced in explanation (9, 10).

Treatment should consist of surgical decompression followed by radiation therapy in all cases with significant neurologic symptoms. Radiation therapy alone has been advocated in early cases with minor symptoms and slow progress.

Case Report: VERTEBRAL HEMANGIOMA OF THE DORSAL SPINE WITH SPINAL CORD COMPRESSION OCCURRING DURING PREGNANCY.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Leo M. Davidoff.

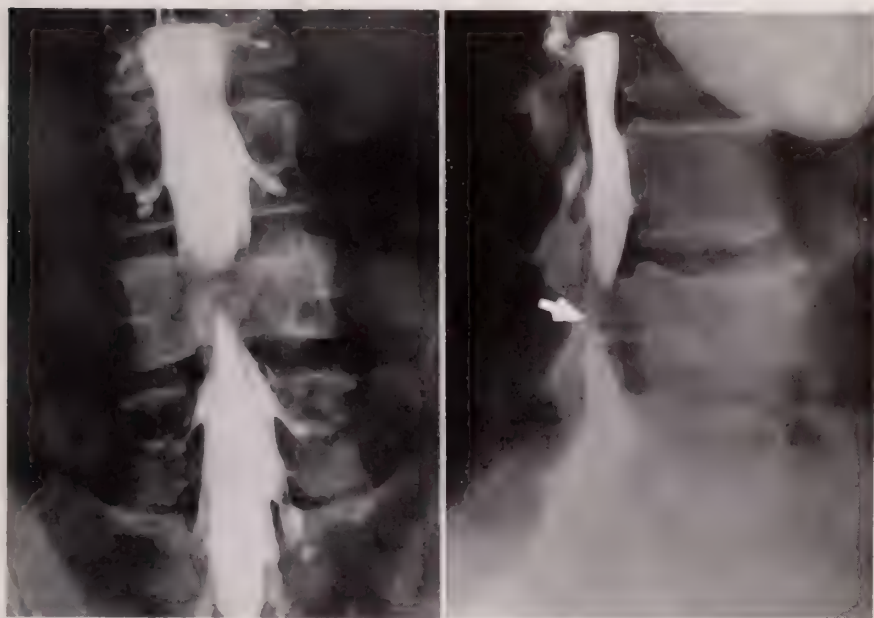
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CASE NO. 187

A 62 year old woman was admitted to the hospital with pain in the low back increasing in severity for about one year. General physical examination was noncontributory. Neurologic examination revealed absent knee jerks and a diminished left ankle jerk.

Radiographic examination of the lumbosacral spine and a lumbar myelogram



Case 187. Fig. 1A. Upright antero-posterior view of the lumbar spine during myelography reveals a defect in the column of opaque material at the level of L4 characteristic of an extradural process. The body of L4 is irregularly sclerotic and partially compressed.

Case 187. Fig. 1B. Upright lateral view at the same examination again reveals the defect in the column. Evidence of mass is seen posterior to the vertebral body (arrow). The changes in the body itself are again noted.

were performed (Fig. 1A and B). The body of L4 was noted to be partially compressed in its supero-inferior diameter and expanded in its antero-posterior diameter. The trabecular pattern was irregularly sclerotic throughout with no localized lytic zones. A partial block to the flow of opaque material was noted during myelography. The characteristics were those of an extradural lesion, and there was evidence of a soft tissue mass behind the vertebral body.

A laminectomy was performed extending from L3 to L5. A lesion was found arising in the body of L4 which displaced the posterior spinal ligament posteriorly and encroached upon the intervertebral foramina. A subtotal removal of the mass was accomplished. The histologic report was that of chordoma.

Case report: CHORDOMA OF L4 WITH PARTIAL INTRASPINAL BLOCK.
See discussion, Case No. 188.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Sydney W. Gross.

CASE NO. 188

A 64 year old male was admitted to the hospital because of severe low back pain radiating into the right buttock, groin and anterior thigh. Symptoms had been present for one month and had failed to respond to conservative therapy. Past history revealed a right nephrectomy for tuberculosis performed 38 years prior to admission. General physical examination was noncontributory except for tenderness to palpation of L3. Neurologic examination revealed a diminished knee jerk on the right.

Radiographic examination of the lumbar spine revealed an extensive destructive process of L3 which involved the vertebral body and the right side of the neural arch and its processes (Fig. 1A and B). Intravenous pyelography revealed a large left kidney. There was slight lobulation to the contour of the lower pole, but the internal structures were unremarkable. The right kidney was absent. Radiographic examination of the chest and skull were normal. A needle biopsy of the right transverse process of L3 was attempted but was unsuccessful. An open biopsy of this region was performed and tumor tissue was obtained from the base of the spinous process of L3. Considerable bleeding was encountered which was controlled with difficulty.

The pathologic differential diagnosis included chordoma, renal cell carcinoma and malignant hemangio-endothelioma. Chordoma was considered most likely despite the absence of typical "physaliphorous" cells. The slides were reviewed independently by two well-known pathologists who confirmed the diagnosis of chordoma.

The patient was discharged from the hospital and referred for a course of Cobalt-60 radiation therapy. A tumor dose of 6,500 r was delivered to a small volume of tissue in three weeks' time via rotational technic. Symptoms were somewhat relieved, sufficient to permit partial ambulation with a brace.

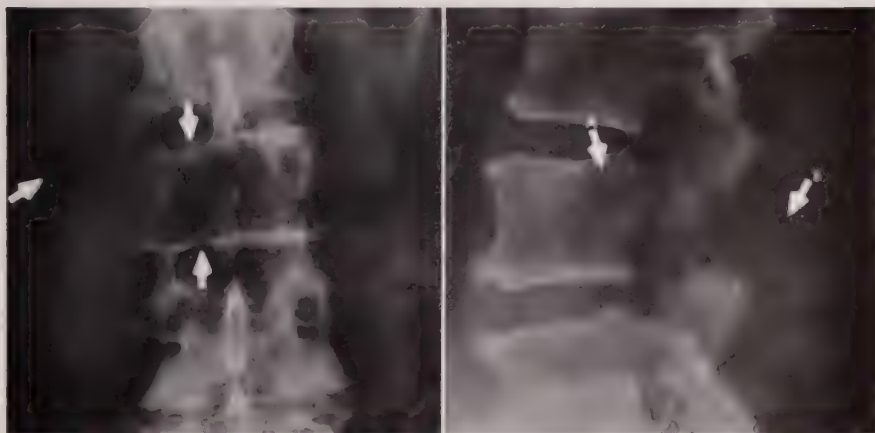
Approximately two months following completion of radiotherapy the patient had pain in the left elbow and radiographic examination revealed a large expanding and destructive lesion of the head and neck of the radius. Two months later the patient had pain in the left orbit with proptosis and secondary glaucoma and enucleation was performed. A tumor mass was encountered behind the globe adjacent to the optic nerve. Histological examination revealed metastatic carcinoma, interpreted as clear cell carcinoma of kidney origin. The original slides were reviewed in the light of these new findings and the diagnosis of chordoma was retracted.

Six weeks later, the patient had a rapidly advancing clinical syndrome of widespread cerebral metastases and expired. Postmortem examination revealed

a large hypernephroma at the lower pole of the left kidney with metastases to brain, skull, lungs, and vertebrae.

DISCUSSION

Chordoma is a malignant tumor which originates in a remnant of notochordal tissue. The tumor is therefore found anywhere along the cranovertebral axis from the sphenoid bone in the region of the dorsum sellae to the coccyx. Combining four reported large series totaling 476 cases, 54 per cent occurred in the sacrococcygeal region, 33 per cent in the spheno-occipital region, and 13 per cent in the cervico-dorso-lumbar spine (1). In the latter group, cervical lesions are more frequent than lumbar lesions, with dorsal lesions least common (1, 2).



Case 188. Fig. 1A. Antero-posterior view of the lumbar spine shows an extensive lesion of L3 involving the body and the right half of the neural arch and its processes (between arrows). A portion of the left pedicle is also involved.

Case 188. Fig. 1B. Lateral view also reveals the destructive process involving the posterior half of the body (arrow A), pedicles and the antero-superior third of the spinous process (arrow B). The adjacent interspaces are preserved.

Typically, chordoma is a slowly growing tumor which is primarily locally invasive and which tends to compress and erode rather than infiltrate. Distant metastases are rare, but a number of instances are known (3). Histologically, the presence of "physaliphorous" cells are pathognomonic and invariably present. However, when only a small biopsy specimen is available, these cells may not be present in the portion of the tumor examined, and pathologic diagnosis then becomes more presumptive and less absolute. Case No. 188 illustrates this difficulty, in which metastatic hypernephroma initially was classified as chordoma. Windeyer's case xv is of interest in this connection (1).

Radiographically the lesion destroys bone and produces a lucent defect which is generally irregular and poorly margined. Soft tissue masses are frequent and often large, particularly in the sacrococcygeal region. Flakes of bone may

be carried into the soft tissues. Calcifications in the tumor may occur (1). There is usually no reactive bone formation or sclerosis in the absence of compression or radiotherapy (4). The appearance produced in Case No. 187 is therefore distinctly unusual; it is unfortunate that no long-term follow-up is available in this case.

Treatment is surgical whenever the tumor is accessible. Radiation therapy is probably of significant palliative value (1).

Case Report: METASTATIC HYPERNEPHROMA TO L4 MASQUERADING AS CHORDOMA.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Paul Keating and Harold Grosselfinger, Good Samaritan Hospital, Suffern, New York.

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CASE NO. 189

A 64 year old female suffered from severe mid-dorsal back pain while reaching out for a heavy object. After two weeks of conservative therapy, the patient was admitted to the hospital.

Radiological examination of the spine revealed marked compression of the body of the 7th dorsal vertebra (Fig. 1A, B). There were numerous tiny lucent defects within the trabecular pattern of the vertebral body, best seen in the lateral projection (Fig. 1B). There was an associated paravertebral soft tissue mass, more prominent on the right side than on the left (Fig. 1A). The right pedicle was thinned out inferiorly, but there was preservation of the adjacent intervertebral spaces. The remaining vertebrae appeared intact.

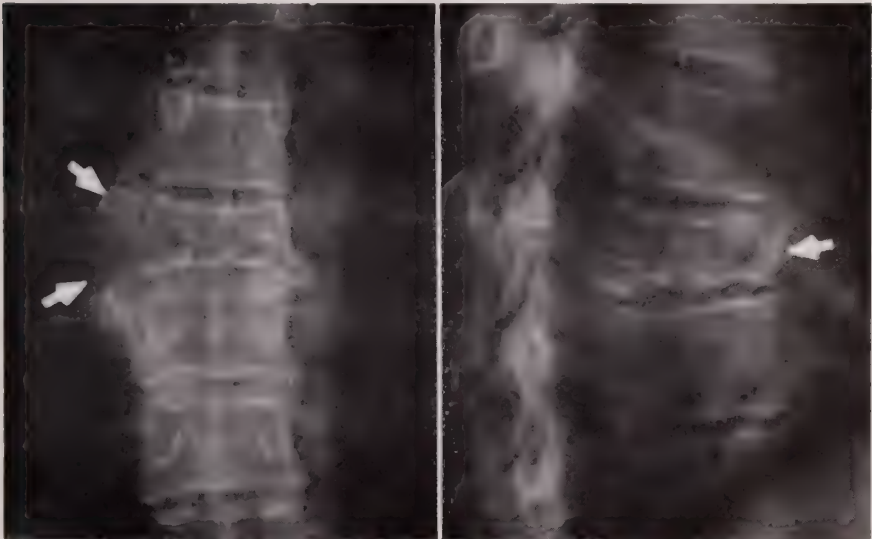
Laboratory examination revealed a normal blood count. There was no albuminuria. Total proteins were 7.6 Gm%, A/G ratio 4.4/3.2 Gm%. Sedimentation rate was 14 mm. hr. Sternal marrow aspiration revealed slight erythroid hyperplasia and 3% plasma cells. No tumor cells were noted.

Within a short time after admission the patient had urinary retention and a sensory level was demonstrable at the level of the 6th dorsal dermatome bilaterally. The upper abdominal reflexes were preserved, the lower ones were absent. There was no motor deficit in the lower extremities. No abnormal reflexes were noted. There was marked tenderness on pressure over the 7th and 8th thoracic spinous processes. Because of fast developing cord compression, a mid-dorsal laminectomy was performed. The spinous process and laminae of D-7 were noted to be soft. The dura under the right pedicle bulged posteriorly displacing the nerve root. There was a vascular brownish-black mass in front and lateral to the dura on the right, small portions of which could be removed by curettage. A wide decompression laminectomy was performed. Pathological

examination revealed plasma cell myeloma. The patient had a slow recovery during which she received radiotherapy to the dorsal region. No long-term follow-up is available for this patient.

DISCUSSION

In most large series of reported cases, involvement of the spine by myeloma represents approximately five per cent of the cases of vertebral lesions producing cord compression (1-3). As a rule the presenting and most striking



Case 189. Fig. 1A. Antero-posterior view of the mid-dorsal region reveals partial collapse of the 7th dorsal vertebral body associated with a paravertebral soft tissue mass (arrows). The inferior border of the right pedicle is thinned out. There is also a bulge in the soft tissues to the left of the spine.

Case 189. Fig. 1B. In the lateral view, the collapsed body is again noted (arrow) with numerous small lucencies seen within the trabecular pattern. The adjoining intervertebral spaces are normal.

symptom is pain in the affected region of the vertebral column. This is then followed by signs and symptoms of a localized myelopathy with a sensory level (4). There is usually no correlation between the degree of vertebral collapse and the rapidity of evolution of the neurological picture (1). When vertebral collapse occurs, even to the point of a real vertebra plana, the adjacent intervertebral discs spaces are spared (5). There is a definite predilection for involvement in the dorsal region (6) and it is very rare for myeloma to affect the extreme proximal or distal ends of the spine. A soft tissue paraspinal mass is frequently present at the site of involvement. The spinal block is usually of the extradural type. At operation, the dura is almost never invaded by the neoplastic tissue, even when completely encircled. Although the prognosis for

neurological recovery is better if the symptoms of cord compression are gradual than when they are sudden in appearance, most cases are benefited by surgical decompression combined with radiotherapy.

Although, as in the case presented, the vertebral myeloma was the only lesion demonstrable by radiography as well as by clinical and laboratory examination, most authors feel that if a patient with solitary myeloma is followed carefully with repeated bone marrow aspirations and electrophoretic studies, eventually it will be possible to demonstrate evidence of dissemination. Well-substantiated cases, however, have been described which have remained localized or "solitary" for over a decade (3-5, 7, 8).

The criteria usually accepted for the diagnosis of solitary myeloma are: 1) only a single lesion demonstrable by radiography; 2) normal bone marrow (under 3% plasma cells); normal hemogram, erythrocyte sedimentation rate and electrophoretic pattern; 4) absent Bence-Jones proteinuria; 5) histologic proof of myeloma cells within the lesion; 6) improvement longer than six months after local treatment (4). Some authorities feel that in certain cases of solitary myeloma there can be minimal abnormalities of the serum electrophoretic pattern and even slight Bence-Jones proteinuria, presumably produced by the plasma cells in the solitary lesion (6). These abnormalities have been known to revert back to normal after local therapy (7).

In the case presented, therefore, the diagnosis of "solitary" myeloma is only presumptive since electrophoretic studies of the serum were not performed and prolonged follow-up examinations are not available.

Case Report: SOLITARY MYELOMA OF THE DORSAL SPINE WITH CORD COMPRESSION.

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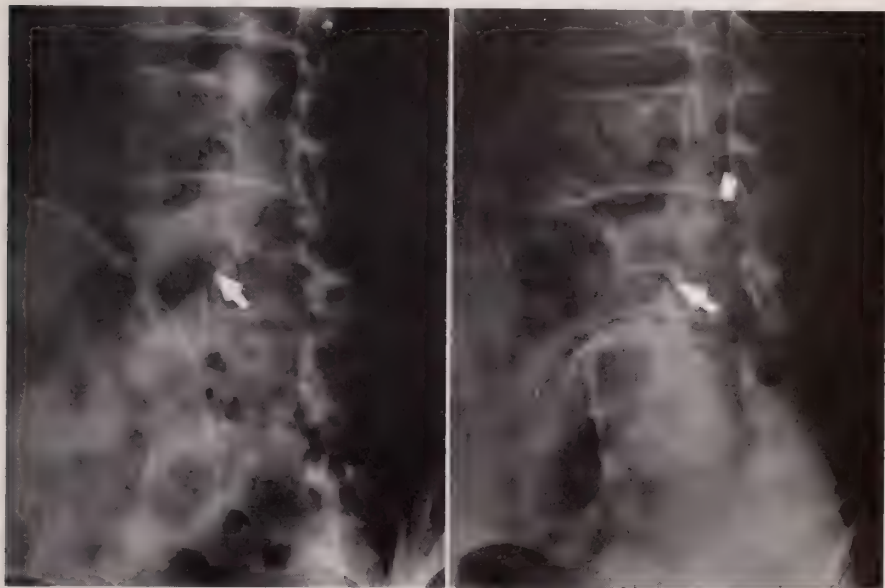
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CASE NO. 190

A 67 year old male complained of the insidious onset of pain in the lower lumbar region and in the posterior aspect of the right hip. No history of trauma could be elicited. Physical examination revealed percussion tenderness in the lumbosacral region. There was considerable referred pain in the right lower

extremity on motion of the lower back. Straight leg raising also produced low back pain. There was slight atrophy of the right calf muscles. The deep tendon reflexes were intact. Laboratory examination of the blood or urine showed no abnormalities.

Radiologic examination of the lumbosacral spine revealed an irregular destructive process involving the pars interarticularis of the 4th lumbar vertebra on the right side, at the junction of the pedicle, lamina and transverse process



Case 190. Fig. 1A. Right posterior oblique view of the lumbosacral spine reveals an irregular destructive lesion involving the pars interarticularis of the 4th lumbar vertebra (arrow). This is located at the junction of the pedicle, lamina and transverse process.

Case 190. Fig. 1B. Left posterior oblique view of the lumbosacral spine (turned around here for clarity) reveals that the comparable area on the left side is entirely normal (arrow) with preservation of sharp cortical margins and no bony destruction.

(Fig. 1A). There was no evidence of surrounding bony sclerosis. The corresponding area on the left side appeared normal (Fig. 1B), as were the vertebral body and spinous process. The bony defect on the right side was better visualized on oblique laminography (Fig. 2). The base of the transverse process was also noted to be thinned out and displaced upwards by the lesion. Lumbar myelogram revealed a partial block at the level of the 4th lumbar vertebra, with a smooth capping defect suggesting an intradural lesion.

At laminectomy, an olive-sized well encapsulated intradural tumor was found at the level of the 4th lumbar vertebra. A portion of the tumor extended through the right intervertebral foramen and was attached to the nerve roots.

After removal of the overlying pedicle, the extension of the tumor was noted to end in *en-dé-sac* fashion just distal to the intervertebral foramen. The entire tumor was removed and a decompression laminectomy was performed. After operation the patient's pain and other symptoms disappeared.

DISCUSSION

Neurofibromas represent approximately thirty per cent of tumors of the spinal cord and its nerve roots (1). Although one-fifth of these are of the



Case 190. Fig. 2. Tomography of the lumbosacral spine in the right posterior oblique position demonstrates clearly a destructive lesion the size of an olive in the pars interarticularis of the 4th lumbar vertebra (between arrows). The base of the transverse process is elevated by this lesion.

"dumbbell" or "hourglass" variety, they are a particular challenge in diagnosis and treatment both to the radiologist and to the neurosurgeon. Most of the dumbbell neurofibromas occur in the cervical and thoracic regions; the lumbosacral region accounts for only five per cent to ten per cent of cases. Two main types of dumbbell neurofibromas are recognized surgically. First, the lesions that are both intradural and extradural in distribution, and second, the extradural ones that extend through the intervertebral canal to become extravertebral in position (2).

The lumbar dumbbell neurofibromas usually first cause symptoms referable to involvement of the affected nerve root. Conversely, in the dorsal region, the initial symptoms are generally those of spinal cord compression. Radiologic

changes in the pars interarticularis, pedicle and lamina are relatively less frequently encountered in dumbbell neurofibromas of the lumbar spine than similar lesions in the cervical region. This may be because the spinal canal and the bony tunnels around the nerve roots in the lumbar region are relatively larger than in the cervical spine.

When the erosion of the pars interarticularis is noted on plain films and laminograms of the spine, myelography is then essential to demonstrate the interspinal portion of the dumbbell tumor. This accurate delineation of the tumor, as in the present case, makes the surgical exploration easier, more direct and accurate.

Case Report: DUMBBELL NEUROFIBROMA OF THE LUMBAR SPINE.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Robert L. Preston and Charles A. Newman.

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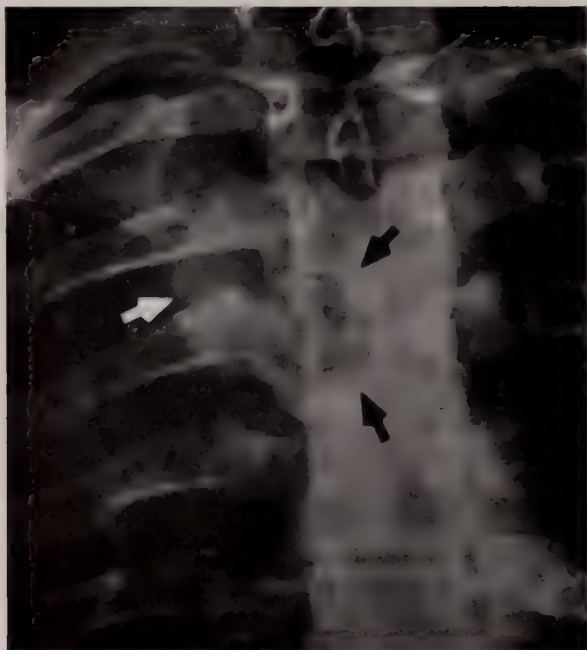
CASE NO. 191

Four years before hospitalization, a 17 year old boy noted the insidious onset of pain and tenderness just to the right of the mid-dorsal spine. One month prior to admission, he noted buckling of the knees and abnormality in gait. No sphincteric disturbances were noted. Examination revealed a broad-based gait. Percussion tenderness of the upper four dorsal vertebrae was elicited. There was weakness of the flexor muscles of the right thigh. Hyperactive deep tendon reflexes in the lower extremities and bilateral Babinski reflexes were noted. There was hypesthesia to pinprick and vibration below the thoracic cage bilaterally. Laboratory examination revealed no abnormalities of the blood or urine. Lumbar puncture showed normal initial pressure; however, a complete block on manometries was noted. The cerebrospinal fluid proteins were 238 mg%.

Radiological examination of the dorsal spine revealed an expanding, well-circumscribed, lucent lesion involving the right half of the neural arch of the 4th dorsal vertebra (Fig. 1A). The pedicle and the transverse process were markedly ballooned by this expanding lesion with preservation of cortical margins (Fig. 1B). The adjoining vertebrae and intervertebral spaces were normal. Myelogram performed via the lumbar route revealed a complete block to the cephalad flow of contrast medium at the level of the 4th dorsal vertebral body. The cap at the block had the characteristic appearance of an extradural lesion.

An upper dorsal laminectomy was performed. The lamina of the 4th dorsal vertebra on the right side was found to be enormously expanded. There was a

defect about one cm in diameter, in the posterior surface of the lamina near the base of the spinous process. After removing the spinous processes of the 4th and 5th dorsal vertebrae, a large cystic cavity was uncovered with walls that were grayish-brown and extremely vascular. There were a few small areas of firm tumor tissue. The lesion extended upward under the lamina of the 3rd dorsal vertebra and downward to the 4th dorsal interspace, causing posterior compression of the dura. A complete decompression and partial removal of the lesion was performed. The patient received radiotherapy to the involved area



Case 191. Fig. 1A. Antero-posterior view of the upper dorsal spine reveals an expanding, well-circumscribed, lucent lesion involving the right side of the neural arch of the 4th dorsal vertebra (between arrows). The margins of the vertebral body can be seen intact overlying this lesion.

in the postoperative period and recovered completely with no residual neurological deficit.

DISCUSSION

Aneurysmal bone cysts affect the spine and long bones with equal frequency (1). They involve all levels of the vertebral column equally, but there is a definite predilection for the lesions to be localized in the posterior arch of the vertebrae. The peak incidence is in the second decade and clinically the presenting symptoms usually are pain and limitation of motion in the affected segment of the spine (2). In one series, however, two-thirds of the patients with aneurysmal bone cyst of the spinal column presented with paraplegia (3).

Radiologically, the lesions are characterized by ballooning of the involved portion of the vertebra with intact cortical borders. Often septa can be demonstrated within the lucent lesion, giving a "soap bubble" appearance. The differential diagnosis is mainly with giant cell tumors, but these latter lesions are very rarely located in the spinal column. On occasion, when the aneurysmal bone cyst becomes very large, it may extend to an adjoining vertebra to involve contiguous pedicles and facets even though it is still benign in nature (2). Sur-



Case 191. Fig. 1B. Oblique view of the same region reveals marked ballooning of the pedicle and transverse process (between arrows) of the 4th dorsal vertebra. The overlying cortex is seen to be intact (upper arrow).

gically, it is important to remove as much of the lesion as possible and to pack it with bone chips, in order to avoid recurrences. Postoperative radiotherapy does not appear to improve the prognosis against local recurrences. At operation, when the shell of bone is removed, the interior of the aneurysmal bone cyst is made up of a honeycombed mass of spaces filled with blood. There is never any arterial type of bleeding within the lesion. Microscopically, the blood-filled cavernous spaces are surrounded by a large amount of osteoid tissue as well as by giant cells. Here, it is important to differentiate it from osteoid osteoma.

Case Report: ANEURYSMAL BONE CYST OF THE DORSAL SPINE WITH CORD COMPRESSION.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Sidney W. Gross.

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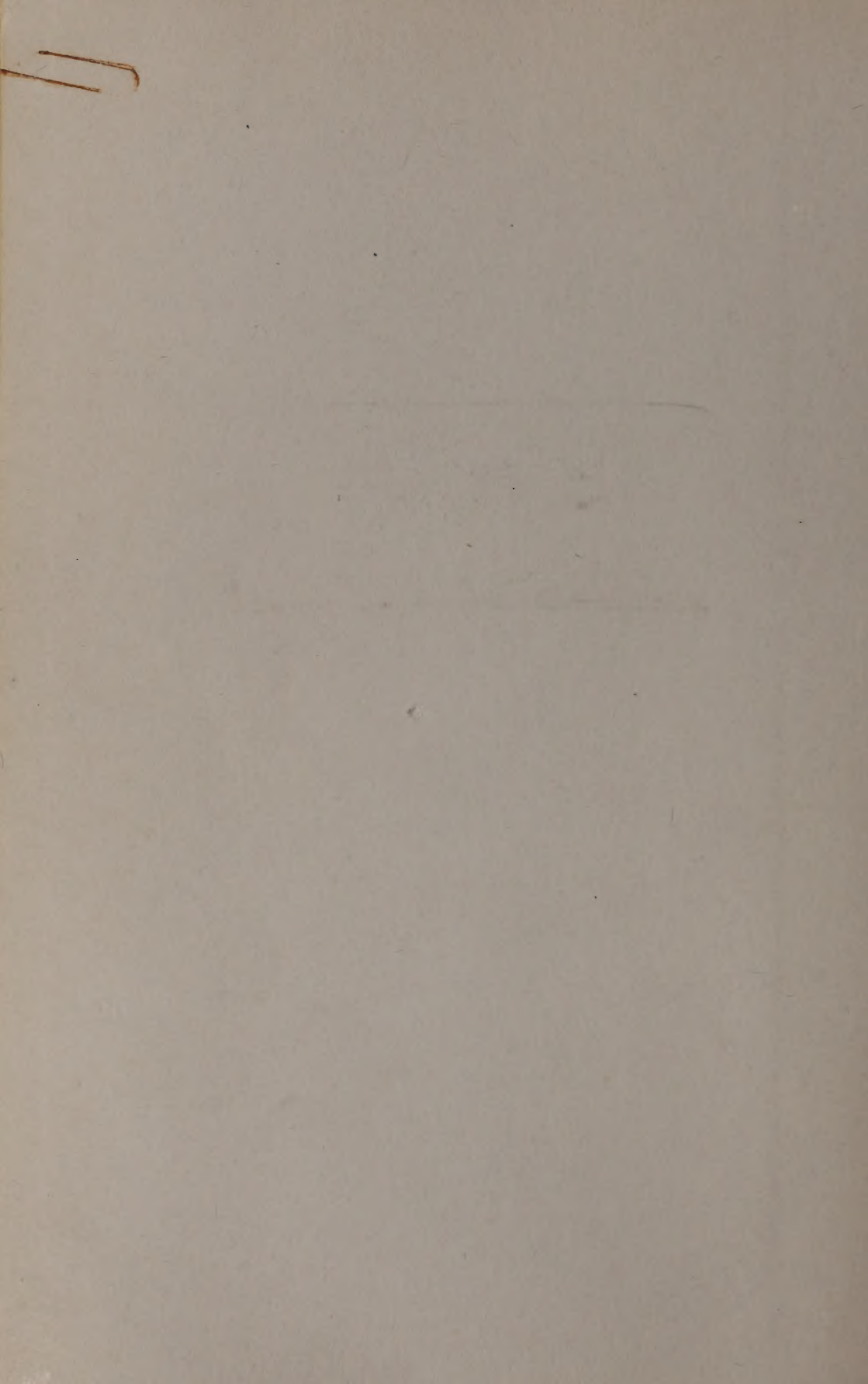
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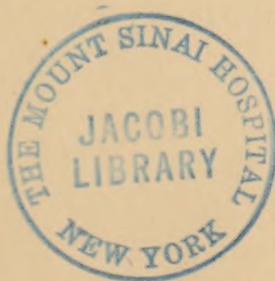
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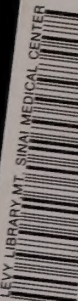
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